NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for NICKEL COMPOUNDS

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Prepared by

Integrated Laboratory Systems
Post Office Box 13501
Research Triangle Park, North Carolina 27709
NIEHS Contract No. N01-ES-25346

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NTP Report on Carcinogens Listing for Nickel Compounds

Carcinogenicity

Nickel compounds are *known to be human carcinogens* based on findings of increased risk of cancers in exposed workers and evidence of malignant tumor formation by multiple routes of exposure at various sites in multiple species of experimental animals. The combined results of epidemiological studies, carcinogenesis studies in rodents, and mechanistic data support the concept that nickel compounds act by the generation of nickel ions at critical sites in target cells of carcinogenesis and allow consideration and evaluation of these compounds as a single group. In 1990, an IARC evaluation of nickel and nickel compounds concluded that "nickel compounds are carcinogenic to humans" (IARC, 1990) based on sufficient evidence for the carcinogenicity of human exposure to nickel compounds as would be found in the nickel refining industry, and very strong evidence of carcinogenicity of a variety of nickel compounds in rodents.

In several cohort studies of workers exposed to various nickel compounds, the risk for death from lung cancer and nasal cancer are elevated (IARC, 1990). Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel refining industries are carcinogenic to humans. IARC (1990) made the overall evaluation of nickel compounds as a group based on indications from animal and mechanistic studies that the generation of ionic nickel in the target site is the event responsible for carcinogenic transformation. Additional study has shown that exposure to soluble nickel compounds alone or in combination with other forms of nickel in nickel refinery workers results in a significant excess risk of lung and nasal cancers and that smoking and nickel had a multiplicative effect (Andersen et al., 1996). Nickel exposure in welders is associated with carcinoma of the trachea, bronchus, and lung in some cases (Simonato, 1991), although these results are complicated by co-exposure to carcinogenic chromium.

Inhalation or intratracheal instillation of nickel subsulfide or nickel oxide has led to a dose-related formation of benign and malignant lung tumors, including carcinomas, in rats and in some studies with mice (IARC, 1990; NTP, 1996a,b). Inhalation of nickel compounds will also result in tumor formation in organs besides the lung, in particular malignant and benign pheochromocytoma in rats (NTP, 1996a,b). Injection of various nickel compounds has been repeatedly reported to produce dose-dependent increases in tumors at a variety of sites in several species of experimental animals. Subcutaneous, intramuscular, intraperitoneal, subperiosteal, intrafemoral, intrapleural, intracerebral, intrarenal, intratesticular and intraocular injections of nickel compounds have all been reported to lead to the formation of malignant tumors at the site of injection. These tumors are usually sarcomas, but other types also develop. Injection of nickel will produce distant tumors in the liver in some strains of mice (IARC, 1990). Soluble nickel acetate is an effective, complete transplacental carcinogen in rats, and brief exposure during pregnancy to this soluble nickel salt will produce malignant pituitary tumors in the offspring. Additionally, transplacental exposure followed by barbital exposure (a known tumor promoter) in the offspring produces renal cortical and pelvic tumors (Diwan et al., 1992). Soluble nickel salts given by injection and followed by barbital resulted in the formation of renal cortical

adenocarcinomas that frequently metastasized to the lung, liver and spleen in adult rats (Kasprzak et al., 1990).

Other Information Relating to Carcinogenesis or Possible Mechanisms of Carcinogenesis

Many studies have shown in cultured animal and human cells that a variety of nickel compounds, including many soluble forms of nickel, damage genetic material. DNA strand breaks, mutations, chromosomal damage, cell transformations and disrupted DNA repair have been observed in *in vitro* studies. Nickel can bind electrovalently to cellular components including DNA. The redox activity of the nickel ion may produce reactive oxygen species that attack DNA and 8-hydroxy-2'-deoxyguanosine can be produced *in vitro* and *in vivo* in target tissues of nickel carcinogenesis (IARC, 1990; Kasprzak et al., 1990). Nickel can induce chromosomal aberrations in exposed human populations. No data are available that indicate the mechanisms thought to account for nickel carcinogenesis in experimental animals would not also operate in humans. The carcinogenic potency of various nickel compounds will vary widely based on solubility properties and speciation. The recent studies indicating that soluble nickel salts can be complete carcinogens (Diwan et al., 1992) and/or initiators of carcinogenesis (Kasprzak et al., 1990) in sites distant from the site of application confirm that ionic nickel is the carcinogenic species.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen;

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded; or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 IDENTIFICATION AND CHEMICAL-PHYSICAL PROPERTIES OF NICKEL AND SELECTED NICKEL COMPOUNDS

Thousands of nickel compounds have been reported in the chemical literature and indexed by Chemical Abstracts Service according to their online Registry File. Scores are reported in the U.S. EPA's Toxic Substances Control Act (TSCA) Inventory. Besides elemental nickel and nickel compounds, workers may come in contact with numerous nickel alloys in fabricating and joining metal products. Selection of compounds to be included in this section, Table 1-1, was based on their potential for occupational exposure outside the research laboratory.

NIOSH (1976, 1990) listed many nickel compounds, alloys, and forms of elemental nickel that are potentially encountered in U.S. workplaces surveyed in the early 1970s and early 1980s. The NIOSH list is presented as Table 2-4. Those compounds in Table 2-4 for which a Chemical Abstracts Service Registry Number (CASRN) could be identified are included in Table 1-1 with the identifying NIOSH number.

The American Chemical Society's *Chemcyclopedia 98* (Rodnan, 1997) provided a list of nickel compounds currently sold in bulk quantities in the United States. These widely used nickel compounds are noted in Table 1-1.

Many nickel salts are available and used primarily as hydrates or aqueous solutions (Antonsen, 1996; Budavari, 1996) whereas the NIOSH list usually indicates an anhydrous form. Thus, both anhydrous and hydrated forms are generally included in Table 1-1 even though properties were often readily available for just the hydrated form.

Water solubilities of the compounds are noted when available. Note that even the extremely insoluble nickel hydroxide hydrate has measurable solubility. It is expected that ionic nickel may arise from any nickel compound at physiological pH.

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, E°C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s
Nickel	7440-02-0	X5918	Ni	58.6934	Lustrous silver-white solid	1453	2732	8.908 (at 20 EC)	Insoluble	Slowly attacked by dilute hydrochloric, sulfuric, and nitric acids. Rendered passive by treatment with concentrated nitric acid.	Finely divided metal reacts with oxygen in air; may be pyrophoric. Decomposes steam at red heat. Not attacked by fused alkali hydroxides. Not expected to solubilize at physiological pH.	Budavari (199 (*The Merck In*
Nickel acetate	373-02-4	81906	$C_4H_8NiO_4$, $Ni(O_2CCH_3)_2$	176.78	Green prismatic crystals	Decomposes	16.6	1.798		Insoluble in ethanol	Decomposition on heating gives NiO.	Budavari (199 Weast (1980) (*CRC Handbc of Chemistry Physics*)
Nickel acetate tetrahydrate	6018-89-9		$C_4H_8NiO_4$; $Ni(O_2CCH_3)_2 \cdot 4H_2O$; $(CH_3CO_2)_2Ni \cdot 4H_2O$	248.84	Green crystalline mass or powder	Decomposes	16	1.744	0.57 M (soluble in 6 parts water)	Soluble in dilute ethanol	Upon heating, loses water of crystallization and then decomposes to NiO.	Budavari (199 Weast (1980); Rodnan (199 (Chemcyclope 98); Antonsen (1996) (*Kirk-Othmer Encyclopedia Chemical Technology, ed.*)
Nickel acetylacetonate; Bisacetylacetonatonickel(II); Bis(2,4-pentanedionato)nickel(II); 2,4-Pentanedione nickel complex	3264-82-2	X5635	$C_{10}H_{14}NiO_4$; $Ni(CH_3COCHCOCH_3)_2$; $Ni(C_5H_7O_2)_2$; $Ni(acac)_2$; $Ni(AA)_2$	256.91	Emerald green orthorhombic crystals.	229-230	220-235 at 11 mm Hg	1.455	Soluble	Soluble in benzene, chloroform, and ethanol. Insoluble in diethyl ether and ligroin.	Exists as a trimer in the solid phase and as a monomer in the vapor phase. Sold in technical and anhydrous grades.	Budavari (199 Rodnan (199
Nickel, ammine[[2,3-butanedione oxime thiosemicarbazonate](2-)]-	16648-35-4	X9871	$C_5H_{11}N_5NiOS$	247.93								

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel ammonium sulfate; Ammonium nickel sulfate; ammonium disulfatonickelate(II); Sulfuric acid, ammonium nickel(2+) salt (2:2:1); Diammonium nickel disulfate	15699-18-0	81907; X4948	$H_8N_2NiO_8S_2$; $Ni(NH_4)_2(SO_4)_2$	286.90								Budavari (1996); Rodnan (1997
Nickel ammonium sulfate hexahydrate	7785-20-8		$H_20N_2NiO_{14}S_2$; $Ni(NH_4)_2(SO_4)_2 \cdot 6H_2O$	394.99	Blue-green crystals			1.923	0.24 M (soluble in 10.4 parts water)	Practically insoluble in ethanol.	A 0.1 M aqueous solution has a pH of 4.6.	Budavari (1996)
Nickel antimony titanate yellow; C.I. Pigment Yellow 53	8007-18-9	M1782	Unspecified	N/A							The NIOSH survey databases list "nickel antimony titanates" with number M1782 (see Table 2-1).	
Nickel bromide; Nickel dibromide	13462-88-9	83009	$NiBr_2$	218.5	Yellow-brown deliquescent crystals	963		5.098 (27 °C)	0.52 M (112.8 g/100 mL)	Soluble in ammonium hydroxide, diethyl ether, and ethanol.	Sublimes in the absence of air.	Budavari (1996); Weast (1980); Rodnan (1997 (no CASRN given)
Nickel bromide trihydrate	7791-20-0		$Br_2H_6NiO_3$; $NiBr_2 \cdot 3H_2O$	272.5	Yellow-green deliquescent needles				2 M (soluble in 1 part water)	Soluble in ammonium hydroxide, diethyl ether, and ethanol.	Begins to lose water of hydration at about 200 °C with complete loss at 300 °C.	Budavari (1996); Weast (1980)
Nickel carbonate; Carbonic acid, nickel salt	16337-84-1		Ni_xCO_3	N/A								Rodnan (1997
Nickel carbonate; Carbonic acid, nickel(2^+) salt (1:1); Nickelous carbonate	3333-67-3	81905	$NiCO_3$	118.72	Light green rhombic crystals	Decompn.			0.78 M (0.0093 g/100 mL)	Soluble in acids.		Weast (1980); Rodnan (1997

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel carbonate; Carbonic acid, nickel(2+) salt (2:1); Nickelous bicarbonate	17237-93-3		$C_2H_2NiO_6$; $Ni(HCO_3)_2$	180.73								Rodnan (1997
Nickel carbonate hydroxide; Basic nickel carbonate	12607-70-4	E0714	$CH_4Ni_3O_7$; $NiCO_3 \cdot 2Ni(OH)_2$; $Ni_3(CO_3)(OH)_4$	304.12								Budavari (1996)
Nickel carbonate hydroxide tetrahydrate; Nickel, (carbonato(2-))tetrahydroxytri-	39340-27-8		$NiCO_3 \cdot 2Ni(OH)_2 \cdot 4H_2O$	376.18	Emerald green cubic crystals, green powder			2.6	Insoluble	Soluble in ammonia, ammonium hydroxide, hot dilute acids with effervescence (decomposes).	The CASRN of the mineral zaratite, which has the same molecular formula, is 1319-49-9.	Budavari (1996); Weast (1980)
Nickel carbonyl; Nickel tetracarbonyl	13463-39-3		C_4NiO_4; $Ni(CO)_4$	170.74	Colorless volatile liquid	-19.3	43	1.318 (17 °C)	1.2 mM (about 5000 parts air-free water)	Soluble in acetone, benzene, carbon tetrachloride, chloroform, and ethanol.	Flammable in air. Explodes at 60 °C.	Budavari (1996); Weast (1980)
Nickel chloride	37211-05-5	50440	Unspecified	N/A								Rodnan (1997
Nickel chloride; Nickel dichloride	7718-54-9	X7161	Cl_2Ni; $NiCl_2$	129.60	Yellow deliquescent scales	1000	Sublimes at 273 °C.	3.55	~0.5 M (64.2 g/100 mL water)	Slightly soluble in ammonium hydroxide and ethanol; insoluble in ammonia.	Readily absorbs ammonia. An aqueous solution is acidic with a pH of about 4.	Budavari (1996); Weast (1980); Rodnan (1997
Nickel chloride hexahydrate	7791-20-0	X4330	$Cl_2H_{12}NiO_6$; $NiCl_2 \cdot 6H_2O$	237.69	Green deliquescent crystals or monoclinic crystalline powder				10.7 M (254 g/100 mL)	Soluble in ethanol.		Budavari (1996); Weast (1980)
Nickel chloride tetrahydrate; Nickel chloride ($NiCl_2$), tetrahydrate	34304-82-0		$Cl_2H_8NiO_4$; $NiCl_2 \cdot 4H_2O$	237.69								Rodnan (1997

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel chromate; Chromic acid (H_2CrO_4), nickel(2+) salt (1:1); Nickel chromate ($NiCrO_4$)	14721-18-7	X4331	$CrNiO_4$; $NiCrO_4$									
Nickel cyanide	557-19-7	82846	C_2N_2Ni; $Ni(CN)_2$	110.73	Yellow-brown solid				Insoluble	Soluble in potassium cyanide.	The usual commercial nickel cyanide contains about 20% to 25% water.	Budavari (1996); Weast (1980)
Nickel cyanide tetrahydrate	13477-95-7		$C_2H_8N_2NiO_4$; $Ni(CN)_2 \cdot 4H_2O$	182.82	Apple-green powder, crystalline plates				Insoluble	Freely soluble in alkali cyanides, in ammonia, and in ammonium carbonate. Slightly soluble in dilute acids.	Loses all water of hydration at 200 °C.	Budavari (1996); Weast (1980)
Nickel di-*N*-butyldithiocarbamate; Nickel dibutyldithiocarbamate; NBC; Nickel, bis(dibutyldithiocarbamato)-	13927-77-0		$C_{18}H_{36}N_2NiS_4$; $Ni[(C_4H_9)_2NCS_2]_2$	467.47	Dark olive-green powder	89-90		1.29	Insoluble	Slightly soluble in benzene and petroleum compounds. Insoluble in ethanol.	Sold in oil-coated powder and granulate forms.	Weast (1980); Rodnan (1997
Nickel dimethyldithiocarbamate; Nickel, bis(dimethylcarbamodithioato-*S,S'*)-, (SP-4-1)-; Bis(dimethyldithiocarbamato)nickel complex	15521-65-0	X4332	$C_6H_{12}N_2NiS_4$; $Ni[(CH_3)_2NCS_2]_2$	299.13								
Nickel dithiocarbamate; Nickel bis(dithiocarbamate); Nickel bis(carbamodithioato-*S,S'*)-, (SP-4-1)-	13985-94-9	83311	$C_2H_4N_2NiS_4$; $Ni(NH_2CS_2)_2$	243.02								
Nickel ferrocyanide; Dinickel hexacyanoferrate	14874-78-3	T1625	$Ni_2Fe(CN)_6$	329.34								
Nickel ferrocyanide [hydrate]	Not found		$Ni_2Fe(CN)_6 \cdot xH_2O$	N/A	Green-white crystals			1.892 (?) [sic]	Insoluble	Soluble in ammonium hydroxide and potassium cyanide; insoluble in hydrochloric acid.	Weast (1980) lists as "nickel ferrocyanide," but gives the hydrate formula.	Weast (1980)

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel ferrocyanide [hydrate]	Not found		$Ni_2Fe(CN)_6 \bullet xH_2O$	N/A	Green-white crystals			1.892 (?) [sic]	Insoluble	Soluble in ammonium hydroxide and potassium cyanide; insoluble in hydrochloric acid.	Weast (1980) lists as "nickel ferrocyanide," but gives the hydrate formula.	Weast (1980)
Nickel fluoride; Nickel difluoride; Nickelous fluoride	10028-18-9	50450	F_2Ni; NiF_2	96.69	Yellowish to green tetragonal crystals (rutile type)	1000		4.72	0.41 M (4 g/100 mL water); sl. soluble	Insoluble in ammonia, diethyl ether, and ethanol	Sublimes in an HF stream above 1000 °C. Decomposes in boiling aqueous solutions.	Weast (1980); Budavari (1996); Antonsen (1996)
Nickel formate; Nickel diformate; Formic acid, nickel(2+) salt	3349-06-2	M4033	$C_2H_2NiO_4$; $Ni(HCOO)_2$	148.73							Decomposes at 180 °C to 200 °C, giving elemental nickel, carbon oxides, hydrogen, methane, and water.	Budavari (1996)
Nickel formate dihydrate	15694-70-9		$C_2H_6NiO_6$; $Ni(HCOO)_2 \bullet 2H_2O$	184.78	Fine green monoclinic crystals	180 decompn.		2.154	Moderately soluble	Insoluble in ethanol and formic acid.	Careful heating at 130 °C to 140 °C gives anhydrous nickel formate.	Budavari (1996); Weast (1980); Antonsen (1996)
Nickel hydroxide; Nickel dihydroxide; Nickelous hydroxide; Nickel(II) hydroxide	12054-48-7	X7142	H_2NiO_2; $Ni(OH)_2$	92.71								Budavari (1996)
Nickel hydroxide monohydrate	1311-07-5		H_4NiO_3; $Ni(OH)_2 \bullet H_2O$	110.73	Apple-green powder (crystals or amorphous)	Decom-poses		4.15	1.4 mM (0.013 g/100 mL water)	Soluble in ammonia and dilute acids.	Decomposes above 200 °C to form nickel monoxide and water. The CAS Registry database lists "green nickel oxide" as a synonym for only this compound. Extremely insoluble in water.	Budavari (1996); Weast (1980); Antonsen (1996)

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel monoxide; Nickel(II) oxide; Nickel protoxide; Nickelous oxide; Nickel(II) oxide, green [or black]	1313-99-1	84269	NiO	74.69	Green (yellow when hot), green-black powder or green cubic crystals	1984; 2090		6.67; 7.45	Insoluble in hot or cold water.	Soluble in acids; slightly soluble in ammonium hydroxide	Color depends on precursor Ni species. Green NiO is formed in Ni refining. Black NiO has slightly more oxygen than the formula indicates (76-77% Ni vs. 78.5% Ni). Black NiO is chief nickel species used to make simple Ni salts.	Budavari (1996); Weast (1990); Rodnan (1997); Antonsen (1985)
Nickel naphthenate; Naphthenic acid(s), nickel salt; Nickel naphthenates	61788-71-4	83650	Unspecified	N/A							Sold as "Nickel naphthenate, -60 in toluene (6-8%)."	ChemFinder database (1998
Nickel nitrate	13138-45-9	50480	N_2NiO_6; $Ni(NO_3)_2$	182.70								Budavari (1996); Rodnan (1997
Nickel nitrate hexahydrate	13478-00-7		$H_{12}N_2NiO_{12}$; $Ni(NO_3)_2 \cdot 6H_2O$	290.81	Green monoclinic, deliquescent crystals	56.7	137	2.05	~8.2 M (238.5 g/L cold water)	Soluble in ammonium hydroxide and ethanol.	The pH of an aqueous solution is about 4.	Budavari (1996); Weast (1980); Rodnan (1997
Nickel octanoate; Nickel(II) octanoate; Nickel bis(2-ethylhexanoate); Nickel octoate	4995-91-9	82957	$C_{16}H_{30}NiO_4$; $[CH_3(CH_2)_6CO_2]_2Ni$	345.10						At least 78% in 2-ethylhexanoic acid.		
Nickel oxalate; Ethanedioic acid, nickel(2^+) salt (1:1)	547-67-1	X7105	C_2NiO_4; NiC_2O_4	146.71								
Nickel oxalate dihydrate	6018-94-6		$C_2H_4NiO_6$; $NiC_2O_4 \cdot 2H_2O$	182.76	Light green powder				Insoluble	Soluble in mineral acids and solutions of ammonium chloride, nitrate, or sulfate; very slightly soluble in oxalic acid.		
Nickel oxide	11099-02-8	50495	Unspecified	N/A							NIOSH lists as "nickel oxides."	

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular Weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel phosphate; Nickel phosphate ($Ni_3(PO_4)_2$); Nickel orthophosphate; Phosphoric acid, nickel(2+) salt (2:3)	10381-36-9	M1709	$N_3O_8P_2$; $Ni_3(PO_4)_2$	366.02							Ignition of nickel phosphate gives the pigment "nickel yellow."	
Nickel phosphate octahydrate; Nickel(2+) orthophosphate octahydrate	19033-89-7		$H_{16}Ni_3O_{16}P_2$; $Ni_3(PO_4)_2 \bullet 8H_2O$	510.20	Apple- or emerald-green plates or granules	Decomposes			Insoluble in hot or cold water	Soluble in acids, ammonia, and ammonium salts.		
Nickel potassium cyanide; Potassium tetracyanonickelate(II); Dipotassium tetrakis(cyano-C)nickelate(2-)	14220-17-8	E0851	$C_4K_2N_4Ni$; $K_2Ni(CN)_4$	240.96	Orange				Soluble	Treating an aqueous solution with hydrogen sulfide will not precipitate nickel sulfide. No CASRN was identified for the orange-yellow, water-soluble monohydrate listed by Budavari (1996).		
Nickel sesquioxide; Nickel oxide (Ni_2O_3); Nickel(III) oxide; Nickelic oxide; Black nickel oxide; Nickel trioxide	1314-06-3		Ni_2O_3	165.39	Gray-black powder				Insoluble	Dissolves in hot sulfuric or nitric acid with oxygen release and in hot hydrochloric acid with chlorine release.	Decomposes at about 600 °C to NiO and O_2.	
Nickel strontium phosphate; Strontium nickel phosphate	34755-21-0	T0477b	$Ni_xSr_xPO_4$	N/A								

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel subsulfide; Nickel sulfide (3:2); Heazlewoodite (mineral); Trinickel disulfide	12035-72-2		Ni_3S_2	240.25	Black powder; pale yellow-bronze metallic lustrous crystals	790		5.82	Insoluble (< 0.1 g/100 mL water)	Soluble in acids. < 0.1 g/100 mL DMSO or ethanol.		U (N F C d
Nickel sulfamate; Sulfamic acid, nickel(2+) salt (2:1)	13770-89-3	50470; Z0110	$H_4N_2NiO_6S_2$; $Ni(OSO_2NH_2)_2$	250.85							Crystalline entity is never isolated from the reaction mixture of Ni or NiO plus hot aqueous sulfamic acid. Forms a tetrahydrate (CASRN 124594-15-6).	F A (
Nickel sulfate	7786-81-4	50510	NiO_4S; $NiSO_4$	154.76	Yellow cubic crystals	Decom-poses		3.68	1.9 M (29.3 g/100 mL)	Insoluble in acetic acid, diethyl ether, and ethanol.	Decomposes at 848 °C.	E (((
Nickel sulfate hexahydrate, "-form	10101-97-0	X4349	$H_{12}NiO_{10}S$; $NiSO_4 \bullet 6H_2O$	262.85	Blue to blue-green tetragonal crystals	Decom-poses		2.07	2.4 M (62.52 g/100 mL)	Soluble in ammonium hydroxide, ethanol, and methanol.	The "-form makes its transition to the $-form at 53.3 °C (the triple point).	E (((
Nickel sulfate hexahydrate, $-form	10101-97-0	X4349	$H_{12}NiO_{10}S$; $NiSO_4 \bullet 6H_2O$	262.85	Opaque blue at room temp.; transparent monoclinic green crystals at 40 °C	Decom-poses		2.07	Soluble	Sparingly soluble in ethanol; more soluble in methanol.	The hexahydrate loses 5 water molecules at about 100 °C. Anhydrous nickel sulfate forms at 280 °C. The aqueous solution has a pH of about 4.5.	E (((
Nickel sulfide; Nickel monosulfide; Millerite (mineral)	11113-75-0	83744	NiS	90.77	Black trigonal crystals or amorphous; yellow metallic luster	797		5.3-5.65	34.8 :M (0.000316 g/100 mL) at 18 °C	Insoluble in acetic acid, diethyl ether, and ethanol.		V F A (

Table 1-1. Chemical and Physical Properties of Nickel and Nickel Compounds (Continued)

Name and Synonyms	CASRN	NIOSH No.	Formula(s)	Molecular weight	Color and Physical State	Melting Point, °C	Boiling Point, °C	Density or Specific Gravity	Solubility in Water, 20-25 °C	Solubility in Other Media	Reactivity/Other Comments	Reference(s)
Nickel tetrafluoroborate; Nickel fluoroborate; Nickel fluoborate; Borate(1$^-$), tetrafluoro-, nickel(2$^+$)	14708-14-6	50460	B_2F_8Ni; $Ni(BF_4)_2$	232.32				1.454	Soluble		Sold in 45% aqueous solution (55-gal drums; tank cars)	R (A
Nickel titanate; Nickel titanium oxide	12653-76-8		NiTiO	154.61								R
Nickel titanate; Nickel titanium oxide ($NiTiO_3$)	12035-39-1	M0778	NiO_3Ti; $NiTiO_3$	154.56								R
Raney Nickel No.7®	7440-02-0		HNi_2; Ni_2H		Gray-black powder or cubic crystals				Insoluble	Insoluble in ethanol.	Note CASRN is that of nickel. Important hydrogenation catalyst prepared by treating Ni-Al alloy with 25% caustic soda solution. Contains hydrogen and residual aluminum. Ignites spontaneously in air. Remains active in storage under a solvent for about 6 months.	E ((

Notes: M = molar mol. wt. = molecular weight N/A = Not applicable

NIOSH No. = The number used by the National Institute of Occupational Safety and Health (NIOSH) in its databases of the National Occupational Hazard Survey and the National Occupational Exposure Survey to identify substances to which workers were potentially exposed. See Table 2-4.

2.0 HUMAN EXPOSURE

2.1 Use

Nickel and its alloys are valued for their strength, corrosion resistance, high ductility, good thermal and electric conductivity, magnetic characteristics, and catalytic properties (NiDI, 1997). In the United States, approximately 200,000 metric tons of nickel (primary plus secondary nickel) are used per year. The use of primary nickel (Table 2-1) is divided into six sectors: (1) stainless steels, (2) alloy steels, (3) nickel alloys, (4) foundry, (5) plating, and (6) other. In 1996, approximately 46% of U.S. primary nickel consumption was for stainless steel and alloy steel production, 33% went into nonferrous alloys and superalloys, 14% into electroplating, and 7% into other uses such as chemicals, catalysts, batteries, coins, pigments, ceramics, eating utensils, and jewelry (Kuck, 1997a; NiDI, 1997).

2.2 Production

2.2.1 Product Classification and Processes

Metallic nickel is produced from sulfide ore and silicate-oxide ore. Neither type of ore contains more than three percent nickel. Sulfide ores are extracted by flotation and magnetic separation into preparations containing nickel and other metals, while silicate-oxide ores are extracted by chemical means. Other ways of obtaining nickel are through the recycling process, consumer scrap, and through the refining of other metals, such as copper and platinum (IARC, 1990).

Nickel products are classified by the amount of nickel they contain. Class I products are defined as containing ≥99.7 percent nickel, whereas Class II products vary in their nickel content (NiDI, 1997). The nickel used in Class I nickel products is refined using a variety of processes to decrease impurities such as antimony, cobalt, arsenic, zinc, copper, iron, and lead. Cobalt closely resembles the physical and chemical properties of nickel and is often difficult to remove completely from the mined ores, therefore many Class I products may contain high levels of cobalt. Nickel products designated as Class II products such as nickel oxide, metallized nickel oxide, and ferronickel are produced directly by smelting and roasting and are sufficiently pure to be used without refining in applications like stainless steel production (Ullman, 1985). Ammonium nickel sulfate is produced by reacting nickel sulfate with ammonium sulfate and crystallizing the salt from a water solution (Antonsen, 1981; Sax and Lewis, 1987; both cited by IARC, 1990). It is produced by three companies in the United Kingdom, two in the United States, and one in Japan (Chemical Information Services, Ltd., 1988; cited by IARC, 1990).

Two commercial processes are used to manufacture nickel carbonyl. The atmospheric method, practiced in the United Kingdom, produces nickel carbonyl by passing carbon monoxide over freshly reduced nickel. In Canada, high-pressure carbon monoxide is used in the formation of iron and nickel carbonyl. These two products are later separated by distillation. The second method, also practiced in the United States, prepares nickel carbonyl by reacting carbon monoxide with nickel sulfate solution (Antonsen, 1996). Nickel carbonyl is manufactured by

Table 2-1. Uses of Nickel and Nickel Compounds

Nickel Compound	Use	Reference
Nickel	Nickel plating for various alloys, for coins, electrotypes, storage batteries, magnets, lightning rod tips, electrical contacts and electrodes, spark plugs, and machinery parts. Also used for hydrogenation of oils and other organic substances.	Budavari (1996); Sax and Lewis (1987; cited by IARC, 1990)
Ammonium nickel sulfate	Electroplating metals, a dye mordant, and in metal finishing compositions.	Budavari (1996); Sax and Lewis (1987; cited by IARC, 1990)
Nickel acetate	Catalyst, mordant for textiles, an intermediate in the formation of other nickel compounds, a sealer for anodized aluminum, and in nickel electroplating.	Budavari (1996); Antonsen (1981; cited by IARC, 1990)
Nickel acetylacetonate	Catalyst	Budavari (1996)
Nickel carbonate hydroxide	Nickel plating, a catalyst for hardening fats, and an ingredient of ceramic colors and glazes.	Budavari (1996)
Nickel carbonyl	Organic synthesis, production of high-purity nickel powder, and continuous nickel coatings on steel and other metals.	Mond et al. (1890); Wilke et al. (1966; both cited by Budavari, 1996)
Nickel chloride	Nickel plating cast zinc, manufacturing sympathetic ink. The anhydrous salt of nickel chloride is used in gas masks to absorb ammonia.	Budavari (1996)
Nickel cyanide	Nickel plating	Budavari (1996)
Nickel dimethylglyoxime	Sun-fast pigment in paints, used in lacquers, cellulose compounds, and cosmetics.	Budavari (1996)
Nickel formate	Manufacturing nickel and preparation of nickel catalysts for organic reactions (mainly hydrogenation catalysts).	Budavari (1996)
Nickel monoxide	Painting on porcelain, manufacturing magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes.	Budavari (1996); Antonsen (1981; cited by IARC, 1990)
Nickel nitrate	Nickel plating and manufacturing brown ceramic colors.	Budavari (1996)
"Nickel yellow" (yield after nickel phosphate is ignited)	Pigment in oil paints and water colors.	Budavari (1996)
Nickel sulfate	Nickel plating, a mordant in dyeing and printing fabrics, and blackening zinc and brass.	Budavari (1996)
Raney nickel®	Catalyst for hydrogenation of unsaturated organic compounds.	Budavari (1996)

two companies in the Federal Republic of Germany, two in the United States, and one in Japan (Chemical Information Services Ltd., 1988; cited by IARC, 1990).

The compound nickel chloride hexahydrate is produced by the reaction of nickel powder or nickel oxide with hot aqueous hydrochloric acid (Antonsen, 1996). It is produced by eight

companies in the United States, six in India, four in the Federal Republic of Germany, four in Japan, four in the United Kingdom, three in Mexico, two in Brazil, two in France, two in Italy, and one in Spain, Switzerland, and Taiwan (Chemical Information Services, Ltd., 1988; cited by IARC, 1990).

Nickel hydroxide is prepared by three processes: 1) treating a nickel sulfate solution with sodium hydroxide to yield a gelatinous nickel hydroxide, which forms a fine precipitate when neutralized; 2) electrodeposition at an inert cathode using metallic nickel as the anode and nickel nitrate as the electrolyte; 3) extraction with hot alcohol of the gelatinous precipitate formed by nickel nitrate solution and potassium hydroxide (Antonsen, 1996).

Nickel monoxide is produced by firing a mixture of pure nickel powder and water in air at 1000 °C or by firing a mixture of high purity nickel powder, nickel oxide, and water in air (Antonsen, 1996). This nickel compound is produced by two companies in the United States, six in Japan, two in the United Kingdom, and one in the Federal Republic of Germany (Chemical Information Services Ltd., 1988; cited by IARC, 1990).

Nickel nitrate hexahydrate is prepared by reacting dilute nitric acid and nickel carbonate. Three methods of manufacturing nickel nitrate hexahydrate on a commercial basis include: 1) slowly adding nickel powder to a stirred mixture of nitric acid and water; 2) a two tank reactor system, one with solid nickel and one with nitric acid and water; 3) adding nitric acid to a mixture of black nickel oxide powder and hot water. Anhydrous nickel nitrate is produced by treating the hexahydrate with fuming nitric acid (Antonsen, 1981; cited by IARC, 1990). Nickel nitrate is produced by six companies in the United States, four in Brazil, four in Japan, four in the United Kingdom, two in the Federal Republic of Germany, two in France, two in India, two in Italy, two in Spain, one in Argentina, Australia, Belgium, Mexico, and Switzerland (Chemical Information Services Ltd., 1988; cited by IARC, 1990).

Nickel subsulfide is prepared by the direct fusion of nickel with sulfur. Nickel sulfide and nickel subsulfide are produced in large quantities as intermediates in the processing of sulfidic and silicate-oxide ores (IARC, 1990).

Anhydrous nickel sulfate is produced by a gas-phase reaction of nickel carbonyl with sulfur dioxide and oxygen at 100 °C or in a closed-looped reactor that recovers the solid product in sulfuric acid. The hydrates are prepared by treating nickel powder, nickel carbonate, or nickel oxide with dilute sulfuric acid (Antonsen, 1981; cited by IARC, 1990). Historically, most nickel sulfate has been produced in Belgium, Czechoslovakia, the Federal Republic of Germany, Finland, Japan, Taiwan, the United Kingdom, the United States, and the Union of Soviet Socialist Republics (ERAMET-SLN, 1989b; cited by IARC, 1990).

2.2.2 Production Volumes

In 1995, the Glenbrook Nickel Company, a subsidiary of Cominco, Ltd., produced 8,300 metric tons of nickel contained in ferronickel from imported ores. In 1996, Glenbrook processed 719,000 metric tons of nickel ore, producing 15,000 metric tons of nickel contained in ferronickel (Cominco, 1998).

The United States imported approximately 3,070 metric tons of metallurgical-grade nickel oxide in 1994, but only 530 metric tons in 1995. The nickel imported in 1995 was approximately

59% of the net nickel consumed. This amount was lower than the amount imported in 1994 because Glenbrook resumed production of ferronickel in 1995 (Kuck, 1997b). U.S. exports of nickel products have increased in recent years because of increased demand for stainless steel in the Far East and Western Europe.

In 1996, 164 facilities reported consumption of nickel (Kuck, 1997a). In the Western World, demand for primary nickel reached an all-time high in 1995 when it increased by 15% (from 786,000 to 900,000 metric tons) over the previous year (Kuck, 1997b).

2.3 Nickel Refining

2.3.1 Refining Processes

Nickel refining is a complex process involving many steps and intermediate compounds. Sulfide ores are initially concentrated mechanically and the concentrates are treated by a series of processes, including roasting, smelting, and converting to produce a copper-nickel matte. The matte is further treated to produce a copper-nickel alloy and nickel sulfide. These are then refined to nickel by electrolysis or the carbonyl process. Lateritic ores may be treated by pyrometallurgical processes followed by reduction or electrolysis. Hydrometallurgical processes involving leaching with ammonia or sulfuric acid may be used also (Tien and Howson, 1985).

Carbonyl refining involves the use of nickel carbonyl as an intermediate. High purity nickel pellets are used for melting and dissolving and are a product of the process. Nickel powders used in chemical syntheses and for making nickel alkaline-battery electrodes and powder-metallurgical parts are also derived from the carbonyl-refining process (Antonsen, 1996). This process is based on the selective action of carbon monoxide gas which reacts with nickel occurring in previously metallized materials or with nickel concentrates separated from copper-nickel matte. At 50 °C, the reaction results in the formation of nickel carbonyl which is easily separated from other metals, such as copper, cobalt, and iron. The carbonyl is brought into contact with surfaces heated to around 200 °C at which point it decomposes, releasing carbon monoxide and yielding pure nickel (Carson, 1980; ICNCM, 1990).

2.3.2 Types of Ores

The type of nickel ore processed varies from region to region. There are two types of nickel ores—sulfide ores and silicate-oxide ores (laterites/garnierites) (IARC, 1990). Sulfide deposits, which are formed far beneath the earth's surface by the reaction of sulfur with nickel-bearing rocks, account for most of the nickel that is produced worldwide. The most common nickel sulfide is pentlandite ($Fe_9Ni_9S_{16}$), which is frequently found in association with chalcopyrite ($CuFeS_2$) and pyrrhotite (Fe_7S_8). Lateritic ores, which are formed over long periods of time as a result of weathering of nickel-containing rocks and found in the form of oxides or silicates (Tien and Howson, 1985) exist in tropical regions and regions that once were tropical, such as parts of the Pacific Northwest (IARC, 1990). Canadian and European refineries process mainly copper-sulfidic nickel ores, whereas refineries that operated in the United States processed silicate and lateritic nickel ores. Sources of ores processed in the United States were Cuban laterites at Port Nickel, Louisiana, laterites found near the California-Oregon border, nickel silicate ores processed near Riddle, Oregon, and ores from the Duluth gabbro of northeastern

Minnesota. The nickel silicate mineral mined by Hanna Nickel Smelting Company at Nickel Mountain near Riddle, Oregon, was garnierite. Garnierite is a complex nickel magnesium silicate associated with iron, cobalt, chromium, and aluminum and was refined at the Hanna facility by dephosphorizing and deoxidizing to produce ferronickel (Carson, 1980). More recently, the Glenbrook (formerly the Hanna Nickel Smelting Co.) smelter produced ferronickel from domestic and imported lateritic ores (Kuck, 1997a,b).

2.3.3 Refining Operations in the United States

Since the first nickel refinery was first successfully operated in 1902, there have been several refineries established in the United States involved in primary nickel production. Amax Nickel, a division of Amax, Inc., refined primary cobalt and pure nickel at Port Nickel (Braithwaite), Louisiana, beginning in 1974. The facility had a capacity of 36,000 metric tons of nickel when operable. Nickel-copper mattes from Botswana, New Caledonia, Australia, and South Africa were processed. LeClerc et al. (1987) and Langer et al. (1980) note that the soil in the French territory of New Caledonia, where nickel has been mined and smelted for more than one hundred years also, contains large amounts of chrysotile asbestos. Crude nickel sulfate was produced by ASARCO electrolytic copper refineries in Washington, Maryland, and Perth Amboy, New Jersey. Beginning in 1954, crude nickel sulfate was refined at Perth Amboy by hot water leaching, air oxidizing, and adjusting the pH with calcium carbonate solution to precipitate iron, precipitating copper and zinc as the sulfides, and crystallizing the purified solution (Busch et al., 1961; cited by Carson 1980).

In 1972, a plant at SEC Corporation in El Paso, Texas, began operations to recover copper and nickel from the liquor discharged from the final evaporation stage in copper sulfate crystallization from copper-refining electrolytes that were bled for purification. At SEC, nickel and copper were extracted by organic solvents and the pH controlled by ammonia additions. After acid-stripping of the solvent extracts, nickel and copper were recovered by electrowinning (Carson, 1980).

Table 2-2 is a summary of operations that are involved in or have been involved in mining, milling, smelting, or refining of nickel that may have potentially exposed workers to nickel compounds. Currently, there are no nickel refining processes carried out in the United States. The nickel smelter, located near Riddle, Oregon, and operated by Glenbrook Nickel Company, had been the only one active in recent years (Kuck, 1997a,b; King, 1998). Glenbrook announced the closing of its nickel smelter and the associated port facility in Coos Bay, Oregon, in January 1998 (Cominco, 1998).

Table 2-2. U.S. & Foreign Mining, Milling, Smelting, and Refining Operations

FACILITY AND LOCATION	TYPE OF MATERIAL PROCESSED	TYPE OF PROCESS	NICKEL SPECIES
United States Operations			
Huntington Alloys, Inc. (nickel refinery), West Virginia	Nickel-copper matte from Canada and/or nickel matte from New Caledonia	ND	Total nickel, metallic nickel, oxidic nickel sulfidic nickel
Hanna Mining & Smelting Operations (later known as Glenbrook), Oregon	Garnierite (a complex nickel magnesium silicate associated with iron, cobalt, chromium, and aluminum)	Refined by dephosphorizing and deoxidizing	Oxidic nickel
Amax Port Nickel Refinery, Louisiana	Nickel-copper mattes from Botswana, New Caledonia, Australia, and South Africa (lateritic and silicate ores)	Hydrometallurgical process, atmospheric sulfuric acid leaching	ND
St. Louis Smelting and Refining Company, Fredricksburg, Missouri	Cobalt	Pressure leaching	Metallic nickel
ASARCO Refineries, Tacoma, Washington; Baltimore, Maryland; Perth Amboy, New Jersey	Copper containing nickel and cobalt	Electrolytic copper refining	Crude nickel sulfate
Foreign Operations			
Mond/INCO Nickel Refinery, Clydach Wales	Nickel-copper matte containing nickel subsulfide, copper sulfide, copper-nickel alloy particles, and minor amounts of cobalt, iron, arsenic and platinum	Carbonyl process	Metallic nickel, oxidic nickel, sulfidic nickel, and soluble nickel
Falconbridge Nickel Refinery, Kristiansand, Norway	Crude nickel-copper sulfides matte from Canada	Hybinette process (until 1978) then chlorine leach process	Nickel subsulfide, nickel-copper alloy, nickel-copper oxide, nickel-copper sulfate
INCO Mining, Smelting and Refining Operations, Ontario, Canada	Nickel-copper matte; sulfidic nickel ores	Electrolytic refining	Total nickel, metallic nickel, oxidic nickel, sulfidic nickel, soluble nickel
Outokumpu Oy Nickel Refinery, Finland	Nickel-copper ore consisting of nickel-copper alloy, nickel subsulfide, and copper sulfide	Atmospheric pressure leaching, electrolytic copper removal, cobalt removal, and nickel electrowinning	Soluble nickel
SocietJ le Nickel's Mining and Smelting Operations, New Caledonia	Lateritic ores including silicate and limonite ores (also contains asbestos)	Mining operations	Nickel silicate, oxidic nickel

ND = No data given Sources: Carson (1980); ICNCM (1990).

2.4 Exposure

2.4.1 Environmental Exposure

Nickel is ubiquitous in nature, occurring mainly in the form of sulfide, oxide, and silicate minerals. Nickel is an essential element in certain microorganisms, animals, and plants and is generally believed also to be an essential element for humans (NiDI, 1997). About 130 million metric tons of nickel have been identified in world resource deposits averaging one percent nickel or greater. Sixty percent of the nickel is in laterites and 40% in sulfide deposits. Additionally, deep-sea resources of nickel exist in manganese crusts and nodules covering large areas of the ocean floor, particularly in the Pacific Ocean (Kuck, 1997a). Small amounts of nickel can be emitted into the atmosphere from forest fires, volcanoes, wind-blown dusts, meteoric dusts, and extremely low amounts from sea spray (IARC, 1990).

Environmental exposures to nickel can occur by breathing air or smoking tobacco containing nickel. Very low levels of nickel can be found in ambient air as a result of releases from manufacturing facilities, oil and coal combustion, sewage sludge incineration, and other sources. Contact with many everyday items such as nickel-containing jewelry, cooking utensils, stainless steel kitchens, and clothing fasteners may expose individuals to nickel. Eating food containing nickel is a major source of exposure for most people. The U.S. Environmental Protection Agency (EPA) estimated that the average adult consumes 100 to 300 μg of nickel per day (USEPA, 1998). Drinking water also contains small amounts of nickel (ATSDR, 1997).

2.4.2 Occupational Exposure

The main route of occupational exposure to nickel is through inhalation and, to a lesser degree, skin contact. Nickel refinery dust is a mixture of many nickel species (IRIS, 1997). Exposure concentrations are in Table 2-3.

The National Institute of Occupational Safety and Health (NIOSH) compiled extensive data on potential occupational exposures to nickel, nickel compounds, and alloys in two surveys. The National Occupational Hazard Survey (NOHS) data (NIOSH, 1976) were collected during the period 1972 to 1974 from a sample of 4,636 businesses employing nearly 900,000 workers for the year 1970. The National Occupational Exposure Survey (NOES) data (NIOSH, 1990) were collected during the period 1981-1983 from a sample of 4,490 businesses employing nearly 1,800,000 workers.

The nickel species for which NIOSH collected data are listed in Table 2-4, presented as four groupings. List 14A includes forms of elemental nickel; 14B, nickel compounds and complexes; 14C, nickel alloys; and 14D, nickel alloys used in welding, soldering, and brazing.

Table 2-5 lists U.S. industries by Standard Industrial Classification (SIC) code in which employees were potentially exposed to the nickel compounds of List B in Table 2-1. The 1972-1974 NOHS estimated that 97,192 employees in 9,351 plants were potentially exposed to nickel compounds. The 1981-1983 NOES estimated that 139,779 employees (of which 30,833 were female) of 7,153 plants were potentially exposed to nickel compounds.

Table 2-6 lists those industries in which employees were potentially exposed specifically to nickel sulfate(s): 13,210 total in 2,205 plants in the NOHS and 57,395 total (12,211 females) in 3,509 plants in the NOES.

Table 2-7 lists those industries in which employees were potentially exposed specifically to nickel oxide(s): 4,916 total in 311 plants (nickel oxide; nickel monoxide) and 51,809 total in 1,800 plants ("nickel oxides") in the NOHS and 18,166 total (5,820 females) in 702 plants in the NOES (nickel oxide).

The NOHS provided an estimate of 116 total employees who were potentially exposed to nickel monosulfide at 14 plants producing steel wire and related products (SIC code 3315).

Potential nickel metal and alloy exposure data for species in Lists A, C, and D of Table 2-1 were also compiled by NIOSH. The NOHS estimated that 163,174 total employees in 12,297 plants were exposed to metallic forms of nickel. The NOES estimated that 901,533 total employees (62,776 females) in 51,007 establishments were exposed to nickel metals and alloys.

Although there are no refineries in operation in the United States at present, there is still concern regarding the effects that past exposures in the nickel refining industry have had or are having on the health of former workers. No estimates of the number of former nickel refinery workers exposed were found for inclusion in this background document.

TABLE 2-3. SUMMARY OF CURRENT NICKEL EXPOSURES IN NICKEL-PRODUCING AND -USING INDUSTRIES

Industry Sector	Range of Exposure Concentrations (mg Ni/m^3)[1]	Range of Mean Aerosol Exposure Concentrations (mg Ni/m^3)[1]	Predominant Species[2]
Mining	0-<1.0	0.003-0.15	SU, O[3]
Milling	0.001-4.0	0.01-<0.70	SU
Smelting	0.001-77.0[4]	0.01-<3.0	SU,O[3]
Refining	0.001-20.0[5]	0.003-~1.50[6]	SU,O,M,SO[7]
Stainless and alloy steels	0-<1.0	0.001-0.10	O,M
Nickel alloy steels	0.001-9.0[8]	0.002-~0.50[9]	O,M
Welding and hot cutting	Trace-7.0[8]	0.001-~0.5[10]	O,M[11]
Nickel plating	Trace-~3.0[12]	0.0004-~0.10	SO[13]
Production of chemicals	0.001-~3.0	0.02-~1.50	SO,O,M
Nickel catalysts	0-26.0[14]	0.004-~1.0[15]	SO,O,M[16]
Ni-cadmium batteries	0-~2.0	0.005-~0.50	O,M,SO
Others	Trace-14.0	Trace-0.5[17]	Mixed

1 'Total' nickel, unless otherwise indicated.
2 M=metallic nickel, O=oxidic nickel, NC=nickel carbonyl, SU=sulphidic nickel, SO=solublenickel salts.
3 Dependent upon the type of ore.
4 Upper limits of ranges for most data sources did not exceed 2.0 mg Ni/m^3.
5 Upper limits of ranges for most data sources did not exceed 5.0 mg Ni/m^3.
6 A few mean aerosol concentrations exceeded 1.5 mg Ni/m^3. The highest mean value reported was 4.84 mg Ni/m^3.
7 Dependent upon the operation and job.
8 Upper limits of ranges for most data sources did not exceed 1 mg Ni/m^3.
9 A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest mean value reported was 3.2 mg Ni/m^3.
10 A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest mean value reported was 3.58 mg Ni/m^3.
11 In some instances, soluble nickel was noted to be present, although it was not the pre-dominant form of nickel found.
12 Upper ranges for most data sources did notexceed 1.0 mg Ni/m^3.
13 In instances where speciation was conducted,insoluble nickel compounds were noted to be present although they were not thepredominant forms of nickel found.
14 Upper ranges for most data sources did notexceed 4.0 mg Ni/m^3.
15 A few mean aerosol concentrations exceeded 1.0 mg Ni/m^3. The highest mean value reported was 1.55 mg Ni/m^3.
16 In addition to potential exposures to oxidic and/or metallic nickel species, sulfidic nickel is also believed to be present in the spent nickel catalyst
17 A few mean aerosol concentrations exceeded 0.5 mg Ni/m^3. The highest value meanreported was 4.1 mg Ni/m^3

Table derived from NiPERA (1996)

TABLE 2-4. GROUPINGS FOR NIOSH SURVEY DATA (NIOSH Number and Name)

NICKEL, METAL, ORE (LIST 14A)

X5986	NI, NICKEL POWDER-MF UNKNOWN
X5918	NI, NICKEL-PURE *
X5096	NICKEL, DUST
X3242	NICKEL, ISOTOPE OF MASS 63

NICKEL COMPOUNDS/COMPLEXES (LIST 14B)

50460	BORATE(1-), TETRAFLUORO-, NICKEL(2+); Nickel tetrafluoroborate *
X4331	CHROMIC ACID, NICKEL(2+) SALT (1:1); Nickel chromate *
X7105	ETHANEDIOIC ACID, NICKEL(2+) SALT (1:1); Nickel oxalate *
M4033	FORMIC ACID, NICKEL(2+) SALT; Nickel formate *
M0101	INORGANIC NICKEL COMPOUNDS
M1990	MAGNESIUM-NICKEL
M3818	NB.NI, NICKEL COMPD. WITH NIOBIUM
81906	NICKEL ACETATE *
X3677	NICKEL ALUMINIDE
T1988	NICKEL AMMONIUM FERROCYANIDE **
81907	NICKEL AMMONIUM SULFATE *
83009	NICKEL BROMIDE *
81905	NICKEL CARBONATE *
50440	NICKEL CHLORIDE *
X7161	NICKEL CHLORIDE (NICL2) *
X4330	NICKEL CHLORIDE (NICL2), HEXAHYDRATE *
82846	NICKEL CYANIDE *
83311	NICKEL DITHIOCARBAMATE *
T0483	NICKEL DITHIOOXYAMIDE **
T1625	NICKEL FERROCYANIDE *
50450	NICKEL FLUORIDE *
X7142	NICKEL HYDROXIDE (NI(OH)2) *
T1660	NICKEL NAPHTHALENE SULFONATE **
83650	NICKEL NAPHTHENATE *
50480	NICKEL NITRATE *
84269	NICKEL OXIDE *
50495	NICKEL OXIDES *
X3115	NICKEL PLATED BRASS
81904	NICKEL SALTS
50470	NICKEL SULFAMATE *
50510	NICKEL SULFATE *
83744	NICKEL SULFIDE *
W0002	NICKEL SULFONATE **
M0778	NICKEL TITANATE *
M1782	NICKEL-ANTIMONY TITANATES *
E0714	NICKEL, (CARBONATO(2-))TETRAHYDROXYTRI-; Nickel carbonate hydroxide *
X9871	NICKEL, AMMINE(2,3-BUTANEDIONE OXIME THIOSEMICARBAZONATE)(2-))- *
84025	NICKEL, BIS(DIBUTYLDITHIOCARBAMATO)- *
X4332	NICKEL, BIS(DIMETHYLCARBAMODITHIOATO-S,S")- *
X5635	NICKEL, BIS(2,4-PENTANEDIONATO-O,O')-, (SP-4-1)-; Nickel acetylacetonate *
E0851	NICKELATE(2-), TETRAKIS(CYANO-C)-, DIPOTASSIUM, (SP-4-1)-; Potassium tetracyanonickelate(II) *
82957	OCTANOIC ACID, NICKEL(2+) SALT; Nickel octanoate *
84725	ORGANIC NICKEL COMPOUNDS
E0671	PHOSPHONIC ACID, ((3,5-BIS(1,1-DIMETHYLETHYL)-4-HYDROXYPHENYL)METHYL)-, MONOETHYL ESTER, NICKEL(2+) SALT (2:1) **
M1709	PHOSPHORIC ACID, NICKEL(2+) SALT (2:3); Nickel phosphate *
Z1115	SODIUM HYDROXIDE-TUNGSTEN-MOLYBDENUM-NICKEL-ALUMINUM OXIDE SOLUTION
X2836	SPINELS, CHROMIUM IRON NICKEL BLACK
T0477	STRONTIUM NICKEL PHOSPHATE; Nickel strontium phosphate *
Z0110	SULFAMATE NICKEL ACID COMPOUND; Nickel sulfamate *
X4948	SULFURIC ACID, AMMONIUM NICKEL(2+) SALT (2:2:1); Nickel ammonium sulfate * (see no. 81907 above)
X4349	SULFURIC ACID, NICKEL(2+) SALT (1:1), HEXAHYDRATE; Nickel sulfate hexahydrate *
M3188	TITANIUM, NICKEL, ANTIMONY COMPLEX

TABLE 2-4. GROUPINGS FOR NIOSH SURVEY DATA (NIOSH Number and Name) (continued)

NICKEL ALLOYS (LIST 14C)

X7858	AG.NI, ALLOY MF-UNKNOWN
X8061	AL.C.CO.CR.CU.FE.MN.MO.NB.NI.SI.TI.W, INCOLOY-MF UNKNOWN
X6385	AL.C.CO.CR.CU.FE.MN.MO.NB.NI.SI.TI, ASTM A637-718
X4908	AL.C.CO.CR.CU.FE.MN.MO.NB.NI.SI.TI, INCONEL-MF UNKNOWN
X6380	AL.C.CO.CR.FE.MN.MO.NB.NI.SI.TI, ASTM B443
X7808	AL.C.CO.CR.FE.MO.NI.TI, AISI 687
X7805	AL.C.CR.FE.MN.MO.NB.NI.SI.TI.ZR,ASTM A567-7V
X7388	AL.CU.FE.MG.MN.NI.SI.SN.ZN-AA 360
X7392	AL.CU.FE.MG.MN.NI.SI.TI.ZN-AA 319
X7394	AL.CU.FE.MG.MN.NI.SI.TI.ZN-AA 333
X7829	AL.CU.FE.MN.NI.PB.SI.SN.ZN, ALLOY MF-UNKNOWN
X6951	AL.CU.FE.MN.NI.SI., CDA 958
X6384	AL.NI, ALLOY-MF UNKNOWN
X7837	AU.NI, ALLOY MF-UNKNOWN
A1278	B.C.CR.FE.N.NI.SI, FERROCHROMIUM-VAN
X6401	C.CO.CR.FE.MN.MO.NI.SI.V.W, HASTELLOY A,B&C
X6378	C.CO.CR.FE.MN.MO.NI.SI.V, AMS 5755
X8048	C.CO.CR.FE.MN.MO.NI.SI.W, AISI 680
X8055	C.CO.CR.FE.MN.MO.NI.SI, HASTELLOY-MF UNKNOWN
X5951	C.CO.CR.FE.MN.NI.SI.W, AISI 670
X7810	C.CO.CR.FE.MN.NI.SI.W, ASTM A567-2
X5905	C.CO.CU.NI.TA.TI.W, ALLOY-MF UNKNOWN
X6391	C.CR.CU.FE.MN.MO.NI.SI, AISI 4140
X7580	C.CR.CU.FE.MN.MO.NI.SI, AISI 4145
X5944	C.CR.CU.FE.MN.MO.NI.SI, AISI 4340
X5953	C.CR.CU.FE.MN.MO.NI.SI, AISI 8620
X7717	C.CR.CU.FE.MN.MO.NI.SI, ASTM A296-CN-7M
X6358	C.CR.CU.FE.MN.MO.NI.SI, STEEL, AISI 4130
X6358	C.CR.CU.FE.MN.MO.NI.SI, STEEL, AISI 4130
X7794	C.CR.CU.FE.MN.NB.NI.SI, AMS 5679
X8124	C.CR.CU.FE.MN.NI.P.SI.ZR, ASTM A242-1
X7796	C.CR.CU.FE.MN.NI.SI.TI, AMS 5675
X5054	C.CR.CU.FE.MN.NI.SI, ASTM B163-600
X7881	C.CR.FE.MB.MN.NI, ALLOY MF-UNKNOWN
X7814	C.CR.FE.MN.MO.N.NI.SI, M2-VAN
X5932	C.CR.FE.MN.MO.NI.SI, AISI E9310
X6377	C.CR.FE.MN.MO.NI.SI, AISI 316
X6361	C.CR.FE.MN.MO.NI.SI, AISI 4330-VAN
X5930	C.CR.FE.MN.NI.P.S.SI, AISI 303
X6379	C.CR.FE.MN.NI.SI.TI, AISI 321
X5938	C.CR.FE.MN.NI.SI, AISI 301
X5937	C.CR.FE.MN.NI.SI, AISI 302
X6376	C.CR.FE.MN.NI.SI, AISI 304
X7800	C.CR.FE.MN.NI.SI, AISI 308
X7871	C.CR.FE.MN.NI.SI, ASTM B344-60NI,16CR.
X8026	C.CR.FE.MN.NI, ALLOY-MF UNKNOWN
X7651	C.CR.FE.MN, ALLOY-MF UNKNOWN
69715	C.CR.FE.MN, STAINLESS STEEL-MF UNKNOWN
X6905	C.CR.FE,MN,MO,NI,SI.V, L6 MF-UNKNOWN
X5936	C.CU.FE.MN.NI.SI, ASTM B160-200
X4282	C.CU.FE.MN.NI.SI, ASTM B164-A
X6373	C.FE.MN.NI.SI.V, AISI W2
X5902	C.FE.MN.NI.SI, DIN 1.3917
X7530	C.FE.MN.NI, STEEL, NICKEL-MF UNKNOWN
M2286	C.I. PIGMENT YELLOW 53
X9111	C.MN.P.S.SI.CR.NI.MO, AISI 316L
X8289	C.NI, NICKEL ALLOY
X7873	CO.FE.NI, ASTM F15
X5059	COBALT ALLOY, CO 46-58,CR 19-21,W 14-16,NI 9-11,FE 0-3,MN 0-2,SI 0-1,C 0-0.2 (AISI 670)
X5061	COBALT ALLOY, CO,C,CR,FE,MN,MO,NI,SI,W (STELLITE)
X6395	CR.FE.MO, ALLOY-MF UNKNOWN
X6371	CR.NI, ALLOY-MF UNKNOWN
X6350	CU.NI.SN, BRONZE, NICKEL-MF UNKNOWN
X6722	CU.NI.ZN, GERMAN SILVER
X6368	CU.NI, ALLOY-MF UNKNOWN
X6398	FE.NI, ALLOY-MF UNKNOWN
X8291	NI.ZN, ALLOY MF-UNKNOWN
X8297	NI.ZR, ALLOY MF-UNKNOWN
50675	NI-HARD STEEL
X8294	NI, NICKEL-FUME-MF UNKNOWN
50420	NI, NICKEL-MF UNKNOWN
X9567	SPINELS, IRON NICKEL BROWN
50676	STEEL, NI-HARD, OXIDES OF

TABLE 2-4. GROUPINGS FOR NIOSH SURVEY DATA (NIOSH Number and Name) (continued)

NICKEL IN WELDING, SOLDERING, BRAZING (LIST 14D)

X7849	AG.NI, ALLOY MF-UNKNOWN, SOLDERING
X7868	AG.NI,ALLOY, MF-UNKNOWN, WELDING
X7743	AL.C.CO.CR.CU.FE.MN.MO.NB.NI.SI.TI, ASTM A637-718, WELDING
X7809	AL.C.CO.CR.FE.MO.NI.TI, AISI 687, WELDING
X7806	AL.C.CR.FE.MN.MO.NB.NI.SI.TI.ZR, ASTM A567-7V, WELDING
X7830	AL.CU.FE.MN.NI.PB.SI.SN.ZN, ALLOY MF-UNKNOWN, WELDING
S2013	ARW NICKEL
S2344	ARW NICKEL ALLOY STEEL
S2222	ARW NICKEL COPPER ALLOYS
S2216	ARW NICKEL/CHROMIUM ALLOY
X7838	AU.NI, ALLOY MF-UNKNOWN, BRAZING
S1026	BRT GOLD/NICKEL
X8132	C.CO.CR.FE.MN.MO.NI.SI.V.W, HASTELLOY A,B&C, WELDING
X7739	C.CO.CR.FE.MN.MO.NI.SI.V, AMS 5755, WELDING
X7741	C.CO.CR.FE.MN.MO.NI.SI.W, AISI 680, WELDING
X7732	C.CO.CR.FE.MN.NI.SI.W, AISI 670, WELDING
X7811	C.CO.CR.FE.MN.NI.SI.W, ASTM A567-2, WELDING
X8119	C.CR.CU.FE.MN.MO.NI.SI., AISI 4140-BRAZING
X8134	C.CR.CU.FE.MN.MO.NI.SI, AISI 4140-WELDING
X7755	C.CR.CU.FE.MN.MO.NI.SI, AISI 8620, WELDING
X7714	C.CR.CU.FE.MN.MO.NI.SI, ASTM A296-CN-7M, WELDING
X7795	C.CR.CU.FE.MN.NB.NI.SI, AMS 5679, WELDING
X8125	C.CR.CU.FE.MN.NI.P.SI.ZR, ASTM A242-1, WELDING
X7797	C.CR.CU.FE.MN.NI.SI.TI, AMS 5675, WELDING
X7781	C.CR.CU.FE.MN.NI.SI, ASTM B163-600, BRAZING
X7766	C.CR.CU.FE.MN.NI.SI, ASTM B163-600, WELDING
X7882	C.CR.FE.MB.MN.NI, ALLOY MF-UNKNOWN, WELDING
X7815	C.CR.FE.MN.MO.N.NI.SI, M2-VAN, WELDING
X7801	C.CR.FE.MN.MO.NI.P.S.SI, AISI 303, WELDING
X7748	C.CR.FE.MN.MO.NI.SI, AISI 316, WELDING
X7876	C.CR.FE.MN.NI.SI.TI, AISI 321, WELDING
X7750	C.CR.FE.MN.NI.SI, AISI 302, WELDING
X7802	C.CR.FE.MN.NI.SI, AISI 304, WELDING
X7798	C.CR.FE.MN.NI.SI, AISI 308, WELDING
X7872	C.CR.FE.MN.NI.SI, ASTM B344-60NI,16CR, WELDING
X8136	C.CU.FE.MN.NI.SI, ASTM B164-A, WELDING
X7826	C.FE.MN.NI, ALLOY MF-UNKNOWN, WELDING
X8128	C.FE.MN.NI, STEEL, NICKEL-MF UNKNOWN, WELDING
X7874	CO.FE.NI, ASTM F15, WELDING
X7745	CR.NI, ALLOY-MF UNKNOWN, WELDING
X7746	CU.NI, ALLOY-MF UNKNOWN, WELDING
S2345	FCA NICKEL ALLOY STEEL
S2223	MIG COPPER-NICKEL ALLOY
S2014	MIG NICKEL
S2217	MIG NICKEL CHROMIUM ALLOYS
X6669	NI, NICKEL-MF UNKNOWN, WELDING
S2015	OFC NICKEL
S2579	OFC NICKEL STEEL
S2218	OFC NICKEL/CHROMIUM ALLOY
S2016	OFW NICKEL
S2219	OFW NICKEL CHROMIUM ALLOYS
S2224	OFW NICKEL COPPER ALLOYS
S2017	OWP NICKEL
S2220	PAC NICKEL/CHROMIUM ALLOY
S2225	REW COPPER/NICKEL
S2018	REW NICKEL
S0039	SOE NICKEL SILVER
S2335	TIG AMS 5679 NICKEL
S2609	TIG AMS 5837 NICKEL
S2019	TIG NICKEL
S2221	TIG NICKEL CHROMIUM ALLOYS
S2226	TIG NICKEL COPPER ALLOYS
S2580	TIG NICKEL STEEL
S2203	TIG, HAST X STEEL (IRON BASED STEEL ALLOY ABOUT 60% IRON, 40% NICKEL)

Notes: * Indicates a nickel compound included in Table 1-1.
** Indicates a compound for which no CASRN was identified; it is not included in Table 1-1.

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS

NATIONAL OCCUPATIONAL HAZARD SURVEY (NOHS) (1972-1974) (NIOSH, 1976)

NICKEL AGGREGATE (LIST 14B IN TABLE 2-4)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
1311	CRUDE PETROLEUM AND NATURAL GAS	29	43	
1511	GENERAL BUILDING CONTRACTORS	43	172	
1711	PLUMBING, HEATING, AIR CONDITIONING	256	9,988	
2052	COOKIES AND CRACKERS	41	41	
2256	KNIT FABRIC MILLS	10	10	
2259	KNITTING MILLS, NEC	8	8	
2284	THREAD MILLS	10	10	
2295	COATED FABRICS, NOT RUBBERIZED	10	80	
2512	UPHOLSTERED HOUSEHOLD FURNITURE	16	16	
2514	METAL HOUSEHOLD FURNITURE	31	94	
2542	METAL PARTITIONS AND FIXTURES	16	16	
2591	VENETIAN BLINDS AND SHADES	37	1,511	
2599	FURNITURE AND FIXTURES, NEC	10	100	
2621	PAPER MILLS, EXCEPT BUILDING PAPER	6	30	
2647	SANITARY PAPER PRODUCTS	27	491	
2711	NEWSPAPERS	126	327	
2721	PERIODICALS	17	291	
2731	BOOK PUBLISHING	90	90	
2741	MISCELLANEOUS PUBLISHING	20	40	
2751	COMMERCIAL PRINTING, EX LITHOGRAPIC	75	150	
2752	COMMERCIAL PRINTING, LITHOGRAPHIC	591	1,464	
2816	INORGANIC PIGMENTS	16	32	
2818	INDUSTRIAL ORGANIC CHEMICALS, NEC	41	187	
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	71	1,202	
2821	PLASTICS MATERIALS AND RESINS	43	1,462	
2822	SYNETHTIC RUBBER	82	815	
2833	MEDICINALS AND BOTANICALS	19	38	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
2844	TOILET PREPARATIONS	47	141	
2851	PAINTS AND ALLIED PRODUCTS	151	4,796	
2871	FERTILIZERS	54	54	
2893	PRINTING INK	43	1,032	
2911	PETROLEUM REFINING	34	888	
3011	TIRES AND INNER TUBES	6	23	
3069	FABRICATED RUBBER PRODUCTS, NEC	19	733	
3079	MISCELLANEOUS PLASTICS PRODUCTS	40	100	
3161	LUGGAGE	3	45	
3211	FLAT GLASS	75	226	
3231	PRODUCTS OF PURCHASED GLASS	21	21	
3269	POTTERY PRODUCTS, NEC	75	3,123	
3273	READY-MIXED CONCRETE	21	21	
3291	ABRASIVE PRODUCTS	173	720	
3312	BLAST FURNACES AND STEEL MILLS	219	4,518	
3315	STEEL WIRE AND RELATED PRODUCTS	14	116	
3321	GRAY IRON FOUNDRIES	86	6,612	
3323	STEEL FOUNDRIES	43	5,237	
3339	PRIMARY NONFERROUS METALS, NEC	26	1,179	
3341	SECONDARY NONFERROUS METALS	14	130	
3351	COPPER ROLLING AND DRAWING	14	327	
3352	ALUMINUM ROLLING AND DRAWING	14	144	
3356	NONFERROUS ROLLING AND DRAWING, NEC	54	499	
3357	NONFERROUS WIRE DRAWING AND INSULATING	11	97	
3362	BRASS, BRONZE, AND COPPER CASTINGS	28	951	
3421	CUTLERY	21	67	
3423	HAND AND EDGE TOOLS, NEC	52	52	
3425	HANDS SAWS AND SAW BLADES	24	48	
3429	HARDWARE, NEC	63	365	
3432	PLUMBING FITTINGS AND BRASS GOODS	35	35	
3433	HEATING EQUIPMENT, EXCEPT ELECTRIC	52	259	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3442	METAL DOORS, SASH, AND TRIM	24	24	
3443	FABRICATED PLATE WORK (BOILER SHOPS)	112	2,030	
3444	SHEET METAL WORK	14	196	
3452	BOLTS, NUTS, RIVETS, AND WASHERS	28	85	
3461	METAL STAMPINGS	183	493	
3471	PLATING AND POLISHING	934	7,665	
3479	METAL COATING AND ALLIED SERVICES	8	24	
3481	MISC. FABRICATED WIRE PRODUCTS	11	76	
3494	VALVES AND PIPE FITTINGS	52	1,141	
3499	FABRICATED METAL PRODUCTS, NEC	64	2,218	
3511	STEAM ENGINES AND TURBINES	39	944	
3522	FARM MACHINERY	11	23	
3533	OIL FIELD MACHINERY	20	40	
3534	ELEVATORS AND MOVING STAIRWAYS	33	198	
3544	SPECIAL DIES, TOOLS, JIGS & FIXTURES	75	276	
3545	MACHINE TOOL ACCESSORIES	50	545	
3554	PAPER INDUSTRIES MACHINERY	78	233	
3559	SPECIAL INDUSTRY MACHINE, NEC	28	284	
3561	PUMPS AND COMPRESSORS	60	4,434	
3569	GENERAL INDUSTRIAL MACHINERY, NEC	11	42	
3573	ELECTRONIC COMPUTING EQUIPMENT	32	54	
3585	REFRIGERATION MACHINERY	17	264	
3589	SERVICE INDUSTRY MACHINES, NEC	14	14	
3599	MISC. MACHINERY, EXCEPT ELECTRICAL	121	242	
3611	ELECTRIC MEASURING INSTRUMENTS	61	683	
3622	INDUSTRIAL CONTROLS	28	313	
3623	WELDING APPARATUS	11	65	
3632	HOUSEHOLD REFRIGERATORS AND FREEZERS	24	141	
3641	ELECTRIC LAMPS	7	382	
3642	LIGHTING FIXTURES	44	267	
3643	CURRENT-CARRYING WIRING DEVICES	50	207	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3644	NONCURRENT-CARRYING WIRING DEVICES	11	11	
3651	RADIO AND TV RECEIVING SETS	6	12	
3652	PHONOGRAPH RECORDS	17	17	
3661	TELEPHONE AND TELEGRAPH APPARATUS	67	2,182	
3662	RADIO AND TV COMMUNICATION EQUIPMENT	26	190	
3673	ELECTRON TUBES, TRANSMITTING	14	650	
3679	ELECTRONIC COMPONENTS, NEC	183	3,689	
3694	ENGINE ELECTRICAL EQUIPMENT	12	2,842	
3711	MOTOR VEHICLES	14	378	
3713	TRUCK AND BUS BODIES	5	5	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	37	173	
3721	AIRCRAFT	34	778	
3722	AIRCRAFT ENGINES AND ENGINE PARTS	5	10	
3729	AIRCRAFT EQUIPMENT, NEC	12	201	
3742	RAILROAD AND STREET CARS	8	32	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	56	576	
3821	MECHANICAL MEASURING DEVICES	81	1,039	
3841	SURGICAL AND MEDICAL INSTRUMENTS	20	78	
3843	DENTAL EQUIPMENT AND SUPPLIES	10	188	
3851	OPHTHALMIC GOODS	36	411	
3871	WATCHES AND CLOCKS	36	222	
3911	JEWELRY, PRECIOUS METAL	32	158	
3912	JEWELERS' FINDINGS AND MATERIALS	18	35	
3914	SILVERWARE AND PLATED WARE	25	225	
3941	GAMES AND TOYS	25	150	
3952	LEAD PENCILS AND ART GOODS	11	55	
3961	COSTUME JEWELRY	11	88	
3963	BUTTONS	25	100	
3964	NEEDLES, PINS, AND FASTENERS	58	517	
3999	MANUFACTURES, NEC	96	224	
4212	LOCAL TRUCKING, WITHOUT STORAGE	220	220	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
4411	DEEP SEA FOREIGN TRANSPORTATION	31	31	
4511	CERTIFICATED AIR TRANSPORTATION	5	375	
4619	PIPE LINES, NEC	8	30	
4721	ARRANGEMENT OF TRANSPORTATION	76	76	
4811	TELEPHONE COMMUNICATION	7	7	
5013	AUTOMOTIVE EQUIPMENT	415	415	
5022	DRUGS, PROPRIETARIES, AND SUNDRIES	282	564	
5211	LUMBER AND OTHER BUILDING MATERIALS	107	107	
5252	FARM EQUIPMENT DEALERS	222	667	
5511	NEW AND USED CAR DEALERS	178	178	
5921	LIQUOR STORES	86	86	
5999	MISCELLANEOUS RETAIL STORES, NEC	232	3,248	
6023	STATE BANKS, NOT FED. RESERVE, FDIC	199	199	
6711	HOLDING COMPANIES	73	146	
7391	RESEARCH & DEVELOPMENT LABORATORIES	668	703	
8061	HOSPITALS	37	37	
TOTAL		9,351	97,192	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

NATIONAL OCCUPATIONAL EXPOSURE SURVEY (NOES) (1981-1983) (NIOSH, 1990)

NICKEL AGGREGATE (LIST 14B IN TABLE 2-4)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
1542	NONRESIDENTIAL CONSTRUCTION, NEC	5	100	25
1743	TERRAZZO, TILE, MARBLE, MOSAIC WORK	464	4,274	
1793	GLASS AND GLAZING WORK	76	227	
2075	SOYBEAN OIL MILLS	18	321	
2079	SHORTENING AND COOKING OILS	17	51	
2091	CANNED AND CURED SEAFOODS	31	31	
2211	WEAVING MILLS, COTTON	166	1,331	832
2221	WEAVING MILLS, SYNTHETICS	23	23	
2241	NARROW FABRIC MILLS	26	385	
2491	WOOD PRESERVING	96	192	
2531	PUBLIC BUILDING & RELATED FURNITURE	12	60	
2751	COMMERCIAL PRINTING, LETTERPRESS	146	1,460	438
2771	GREETING CARD PUBLISHING	20	336	173
2791	TYPESETTING	5	5	
2812	ALKALIES AND CHLORINE	38	383	115
2822	SYNTHETIC RUBBER	15	679	139
2831	BIOLOGICAL PRODUCTS	46	511	325
2841	SOAP AND OTHER DETERGENTS	11	723	
2869	INDUSTRIAL ORGANIC CHEMICALS, NEC	3	3	3
2899	CHEMICAL PREPARATIONS, NEC	97	1,201	54
3069	FABRICATED RUBBER PRODUCTS, NEC	180	6,869	156
3079	MISCELLANEOUS PLASTICS PRODUCTS	304	2,338	102
3229	PRESSED AND BLOWN GLASS, NEC	66	2,415	1,660
3264	PORCELAIN ELECTRICAL SUPPLIES	5	43	
3312	BLAST FURNACES AND STEEL MILLS	22	2,566	
3315	STEEL WIRE AND RELATED PRODUCTS	33	658	
3341	SECONDARY NONFERROUS METALS	14	1,334	14
3351	COPPER ROLLING AND DRAWING	3	3	
3356	NONFERROUS ROLLING AND DRAWING, NEC	10	58	

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3369	NONFERROUS FOUNDRIES, NEC	91	1,066	75
3412	METAL BARRELS, DRUMS, AND PAILS	10	21	
3421	CUTLERY	72	360	
3423	HAND AND EDGE TOOLS, NEC	120	698	41
3429	HARDWARE, NEC	35	484	57
3432	PLUMBING FITTINGS AND BRASS GOODS	27	460	54
3433	HEATING EQUIPMENT, EXCEPT ELECTRIC	21	42	
3442	METAL DOORS, SASH, AND TRIM	31	123	
3443	FABRICATED PLATE WORK (BOILER SHOPS)	5	268	
3444	SHEET METAL WORK	21	62	
3446	ARCHITECTURAL METAL WORK	23	136	
3465	AUTOMOTIVE STAMPINGS	35	366	10
3471	PLATING AND POLISHING	1,177	21,023	3,955
3484	SMALL ARMS	7	163	7
3494	VALVES AND PIPE FITTINGS	53	452	114
3495	WIRE SPRINGS	7	85	
3496	MISC. FABRICATED WIRE PRODUCTS	29	88	29
3511	TURBINES AND TURBINE GENERATOR SETS	3	145	
3519	INTERNAL COMBUSTION ENGINES, NEC	44	15,486	4,352
3523	FARM MACHINERY AND EQUIPMENT	4	103	21
3541	MACHINE TOOLS, METAL CUTTING TYPES	21	270	
3546	POWER DRIVEN HAND TOOLS	19	171	
3547	ROLLING MILL MACHINERY	22	132	44
3549	METALWORKING MACHINERY, NEC	25	279	
3551	FOOD PRODUCTS MACHINERY	65	130	
3552	TEXTILE MACHINERY	11	45	
3554	PAPER INDUSTRIES MACHINERY	7	2,995	22
3555	PRINTING TRADES MACHINERY	27	189	81
3561	PUMPS AND PUMPING EQUIPMENT	60	4,771	8
3562	BALL AND ROLLER BEARINGS	3	259	29
3563	AIR AND GAS COMPRESSORS	43	86	
3572	TYPEWRITERS	4	29	
3573	ELECTRONIC COMPUTING EQUIPMENT	96	2,031	481
3579	OFFICE MACHINES, NEC	14	251	44

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3585	REFRIGERATION AND HEATING EQUIPMENT	12	601	301
3612	TRANSFORMERS	50	1,115	87
3621	MOTORS AND GENERATORS	43	444	315
3622	INDUSTRIAL CONTROLS	38	227	76
3629	ELECTRICAL INDUSTRIAL APPARATUS, NEC	80	1,603	240
3631	HOUSEHOLD COOKING EQUIPMENT	35	209	
3634	ELECTRIC HOUSEWARES AND FANS	53	695	84
3635	HOUSEHOLD VACUUM CLEANERS	6	53	6
3643	CURRENT-CARRYING WIRING DEVICES	177	779	623
3652	PHONOGRAPH RECORDS	163	347	
3661	TELEPHONE AND TELEGRAPH APPARATUS	17	793	272
3662	RADIO AND TV COMMUNICATION EQUIPMENT	38	543	188
3671	ELECTRON TUBES, RECEIVING TYPE	17	256	146
3672	CATHODE RAY TELEVISION PICTURE TUBES	2	9	5
3673	ELECTRON TUBES, TRANSMITTING	37	1,174	217
3674	SEMICONDUCTORS AND RELATED DEVICES	39	2,740	2,011
3678	ELECTRONIC CONNECTORS	9	233	28
3679	ELECTRONIC COMPONENTS, NEC	244	1,888	704
3691	STORAGE BATTERIES	27	485	27
3693	X-RAY APPARATUS AND TUBES	17	17	
3694	ENGINE ELECTRICAL EQUIPMENT	6	470	24
3699	ELECTRICAL EQUIPMENT & SUPPLIES, NEC	55	718	
3711	MOTOR VEHICLES AND CAR BODIES	54	4,820	172
3713	TRUCK AND BUS BODIES	33	69	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	219	2,146	26
3721	AIRCRAFT	22	637	40
3724	AIRCRAFT ENGINES AND ENGINE PARTS	56	830	84
3728	AIRCRAFT EQUIPMENT, NEC	108	877	19
3731	SHIP BUILDING AND REPAIRING	3	28	3
3743	RAILROAD EQUIPMENT	8	278	
3761	GUIDED MISSILES AND SPACE VEHICLES	10	81	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	24	410	
3822	ENVIRONMENTAL CONTROLS	19	970	155
3825	INSTRUMENTS TO MEASURE ELECTRICITY	21	7,296	3,593

TABLE 2-5. POTENTIAL OCCUPATIONAL EXPOSURE ESTIMATES FOR NICKEL COMPOUNDS FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3829	MEASURING & CONTROLLING DEVICES, NEC	10	709	21
3851	OPHTHALMIC GOODS	55	3,917	3,144
3861	PHOTOGRAPHIC EQUIPMENT AND SUPPLIES	35	411	
3873	WATCHES, CLOCKS, AND WATCHCASES	25	198	148
3911	JEWELRY, PRECIOUS METAL	365	3,654	932
3914	SILVERWARE AND PLATED WARE	10	392	90
3949	SPORTING AND ATHLETIC GOODS, NEC	7	609	217
3953	MARKING DEVICES	11	121	
3961	COSTUME JEWELRY	112	448	
3964	NEEDLES, PINS, AND FASTENERS	87	857	181
4226	SPECIAL WAREHOUSING AND STORAGE, NEC	77	687	303
4511	CERTIFICATED AIR TRANSPORTATION	3	139	
4582	AIRPORTS AND FLYING FIELDS	6	244	
4583	AIRPORT TERMINAL SERVICES	3	131	
7391	RESEARCH & DEVELOPMENT LABORATORIES	97	8,723	1,143
8062	GENERAL MEDICAL & SURGICAL HOSPITALS	318	2,849	1,749
TOTAL		7,153	139,779	30,833

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS

NATIONAL OCCUPATIONAL HAZARD SURVEY (NOHS) (1972-1974) (NIOSH, 1976)

CAS #	RTECS #	HAZ	DESCRIPTION
7786-81-4	QR9350000	50510	NICKEL SULFATE

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
2295	COATED FABRICS, NOT RUBBERIZED	10	80	
2514	METAL HOUSEHOLD FURNITURE	16	47	
2542	METAL PARTITIONS AND FIXTURES	16	16	
2599	FURNITURE AND FIXTURES, NEC	10	100	
2721	PERIODICALS	17	291	
2818	INDUSTRIAL ORGANIC CHEMICALS, NEC	21	166	
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	14	532	
3161	LUGGAGE	3	45	
3269	POTTERY PRODUCTS, NEC	11	44	
3291	ABRASIVE PRODUCTS	152	678	
3339	PRIMARY NONFERROUS METALS, NEC	11	133	
3421	CUTLERY	21	62	
3423	HAND AND EDGE TOOLS, NEC	52	52	
3429	HARDWARE, NEC	63	365	
3432	PLUMBING FITTINGS AND BRASS GOODS	35	35	
3433	HEATING EQUIPMENT, EXCEPT ELECTRIC	52	207	
3442	METAL DOORS, SASH, AND TRIM	24	24	
3444	SHEET METAL WORK	14	196	
3452	BOLTS, NUTS, RIVETS, AND WASHERS	28	85	
3461	METAL STAMPINGS	161	471	
3471	PLATING AND POLISHING	641	4,065	
3479	METAL COATING AND ALLIED SERVICES	8	24	
3481	MISC. FABRICATED WIRE PRODUCTS	11	76	
3499	FABRICATED METAL PRODUCTS, NEC	17	168	
3511	STEAM ENGINES AND TURBINES	13	53	
3534	ELEVATORS AND MOVING STAIRWAYS	33	66	
3559	SPECIAL INDUSTRY MACHINE, NEC	28	284	
3585	REFRIGERATION MACHINERY	17	264	

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3599	MISC. MACHINERY, EXCEPT ELECTRICAL	96	192	
3611	ELECTRIC MEASURING INSTRUMENTS	44	178	
3622	INDUSTRIAL CONTROLS	11	33	
3632	HOUSEHOLD REFRIGERATORS AND FREEZERS	24	47	
3643	CURRENT-CARRYING WIRING DEVICES	50	190	
3661	TELEPHONE AND TELEGRAPH APPARATUS	61	1,061	
3662	RADIO AND TV COMMUNICATION EQUIPMENT	26	190	
3673	ELECTRON TUBES, TRANSMITTING	14	41	
3679	ELECTRONIC COMPONENTS, NEC	19	245	
3694	ENGINE ELECTRICAL EQUIPMENT	12	37	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	13	40	
3721	AIRCRAFT	8	32	
3729	AIRCRAFT EQUIPMENT, NEC	12	201	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	17	87	
3821	MECHANICAL MEASURING DEVICES	57	660	
3841	SURGICAL AND MEDICAL INSTRUMENTS	20	78	
3871	WATCHES AND CLOCKS	36	219	
3912	JEWELERS' FINDINGS AND MATERIALS	18	35	
3914	SILVERWARE AND PLATED WARE	25	225	
3961	COSTUME JEWELRY	11	88	
3963	BUTTONS	25	100	
3964	NEEDLES, PINS, AND FASTENERS	47	506	
3999	MANUFACTURES, NEC	51	61	
4511	CERTIFICATED AIR TRANSPORTATION	5	30	
7391	RESEARCH & DEVELOPMENT LABORATORIES	5	5	
TOTAL		2,205	13,210	

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS (continued)

NATIONAL OCCUPATIONAL EXPOSURE SURVEY (NOES) (1981-1983) (NIOSH, 1990)

NICKEL SULFATE AGGREGATE
(HAZ CODES 50510, X4349 & X4948)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
2091	CANNED AND CURED SEAFOODS	31	31	
2491	WOOD PRESERVING	96	192	
2531	PUBLIC BUILDING & RELATED FURNITURE	12	60	
2791	TYPESETTING	5	5	
2831	BIOLOGICAL PRODUCTS	46	511	325
2841	SOAP AND OTHER DETERGENTS	11	723	
3079	MISCELLANEOUS PLASTICS PRODUCTS	253	759	
3229	PRESSED AND BLOWN GLASS, NEC	37	441	
3264	PORCELAIN ELECTRICAL SUPPLIES	5	43	
3351	COPPER ROLLING AND DRAWING	3	3	
3369	NONFERROUS FOUNDRIES, NEC	91	1,066	75
3412	METAL BARRELS, DRUMS, AND PAILS	10	21	
3421	CUTLERY	72	360	
3423	HAND AND EDGE TOOLS, NEC	120	645	41
3429	HARDWARE, NEC	35	451	57
3432	PLUMBING FITTINGS AND BRASS GOODS	27	460	54
3471	PLATING AND POLISHING	940	16,041	3,701
3484	SMALL ARMS	7	163	7
3494	VALVES AND PIPE FITTINGS	53	452	114
3496	MISC. FABRICATED WIRE PRODUCTS	29	88	29
3511	TURBINES AND TURBINE GENERATOR SETS	3	145	
3523	FARM MACHINERY AND EQUIPMENT	4	62	
3546	POWER DRIVEN HAND TOOLS	19	171	
3547	ROLLING MILL MACHINERY	22	132	44
3554	PAPER INDUSTRIES MACHINERY	7	2,995	22
3561	PUMPS AND PUMPING EQUIPMENT	8	40	8

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS(continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3563	AIR AND GAS COMPRESSORS	43	43	
3572	TYPEWRITERS	4	29	
3573	ELECTRONIC COMPUTING EQUIPMENT	85	1,048	441
3579	OFFICE MACHINES, NEC	14	251	44
3621	MOTORS AND GENERATORS	2	35	28
3622	INDUSTRIAL CONTROLS	38	227	76
3631	HOUSEHOLD COOKING EQUIPMENT	35	209	
3634	ELECTRIC HOUSEWARES AND FANS	53	695	84
3635	HOUSEHOLD VACUUM CLEANERS	6	53	6
3661	TELEPHONE AND TELEGRAPH APPARATUS	14	212	50
3662	RADIO AND TV COMMUNICATION EQUIPMENT	12	265	52
3671	ELECTRON TUBES, RECEIVING TYPE	6	126	108
3673	ELECTRON TUBES, TRANSMITTING	22	133	88
3674	SEMICONDUCTORS AND RELATED DEVICES	14	584	311
3678	ELECTRONIC CONNECTORS	9	233	28
3679	ELECTRONIC COMPONENTS, NEC	81	1,535	701
3693	X-RAY APPARATUS AND TUBES	17	17	
3694	ENGINE ELECTRICAL EQUIPMENT	6	470	24
3711	MOTOR VEHICLES AND CAR BODIES	3	511	11
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	189	2,017	26
3721	AIRCRAFT	16	316	17
3724	AIRCRAFT ENGINES AND ENGINE PARTS	6	141	3
3728	AIRCRAFT EQUIPMENT, NEC	106	840	19
3731	SHIP BUILDING AND REPAIRING	3	10	
3743	RAILROAD EQUIPMENT	3	3	
3761	GUIDED MISSILES AND SPACE VEHICLES	7	72	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	24	410	
3822	ENVIRONMENTAL CONTROLS	19	970	155
3825	INSTRUMENTS TO MEASURE ELECTRICITY	21	6,157	3,069
3829	MEASURING & CONTROLLING DEVICES, NEC	10	709	21
3851	OPHTHALMIC GOODS	55	55	
3861	PHOTOGRAPHIC EQUIPMENT AND SUPPLIES	8	38	
3873	WATCHES, CLOCKS, AND WATCHCASES	25	198	148
3911	JEWELRY, PRECIOUS METAL	317	3,199	886

TABLE 2-6. POTENTIAL NICKEL SULFATE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS(continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3861	PHOTOGRAPHIC EQUIPMENT AND SUPPLIES	8	38	
3873	WATCHES, CLOCKS, AND WATCHCASES	25	198	148
3911	JEWELRY, PRECIOUS METAL	317	3,199	886
3914	SILVERWARE AND PLATED WARE	10	392	90
3953	MARKING DEVICES	11	121	
3961	COSTUME JEWELRY	112	448	
3964	NEEDLES, PINS, AND FASTENERS	23	544	181
4511	CERTIFICATED AIR TRANSPORTATION	3	65	
4582	AIRPORTS AND FLYING FIELDS	3	162	
7391	RESEARCH & DEVELOPMENT LABORATORIES	53	6,853	895
8062	GENERAL MEDICAL & SURGICAL HOSPITALS	72	940	172
TOTAL		3,509	57,395	12,211

TABLE 2-7. POTENTIAL NICKEL OXIDE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS

NATIONAL OCCUPATIONAL HAZARD SURVEY (NOHS) (1972-1974) (NIOSH, 1976)

CAS #	RTECS #	HAZ	DESCRIPTION
1313-99-1	QR8400000	84269	**NICKEL OXIDE**

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	14	350	
2821	PLASTICS MATERIALS AND RESINS	43	1,462	
2851	PAINTS AND ALLIED PRODUCTS	47	1,744	
3269	POTTERY PRODUCTS, NEC	49	98	
3339	PRIMARY NONFERROUS METALS, NEC	26	210	
3433	HEATING EQUIPMENT, EXCEPT ELECTRIC	52	104	
3673	ELECTRON TUBES, TRANSMITTING	14	14	
3679	ELECTRONIC COMPONENTS, NEC	19	697	
3911	JEWELRY, PRECIOUS METAL	32	158	
3952	LEAD PENCILS AND ART GOODS	11	55	
7391	RESEARCH & DEVELOPMENT LABORATORIES	5	25	
TOTAL		311	4,916	

CAS #	RTECS #	HAZ	DESCRIPTION
		50495	**NICKEL OXIDES**

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
1711	PLUMBING, HEATING, AIR CONDITIONING	256	9,988	
2816	INORGANIC PIGMENTS	16	32	
2818	INDUSTRIAL ORGANIC CHEMICALS, NEC	21	21	
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	45	431	
2822	SYNTHETIC RUBBER	20	79	
2911	PETROLEUM REFINING	19	151	
3079	MISCELLANEOUS PLASTICS PRODUCTS	11	23	

TABLE 2-7. POTENTIAL NICKEL OXIDE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3269	POTTERY PRODUCTS, NEC	26	2,981	
3312	BLAST FURNACES AND STEEL MILLS	185	4,328	
3321	GRAY IRON FOUNDRIES	75	6,568	
3323	STEEL FOUNDRIES	43	5,237	
3339	PRIMARY NONFERROUS METALS, NEC	11	564	
3341	SECONDARY NONFERROUS METALS	14	130	
3351	COPPER ROLLING AND DRAWING	14	327	
3356	NONFERROUS ROLLING AND DRAWING, NEC	54	360	
3362	BRASS, BRONZE, AND COPPER CASTINGS	28	951	
3443	FABRICATED PLATE WORK (BOILER SHOPS)	112	2,030	
3494	VALVES AND PIPE FITTINGS	52	1,141	
3499	FABRICATED METAL PRODUCTS, NEC	48	2,050	
3511	STEAM ENGINES AND TURBINES	25	891	
3533	OIL FIELD MACHINERY	20	40	
3544	SPECIAL DIES, TOOLS, JIGS & FIXTURES	14	42	
3545	MACHINE TOOL ACCESSORIES	50	495	
3554	PAPER INDUSTRIES MACHINERY	78	233	
3561	PUMPS AND COMPRESSORS	60	4,413	
3569	GENERAL INDUSTRIAL MACHINERY, NEC	11	42	
3599	MISC. MACHINERY, EXCEPT ELECTRICAL	25	50	
3611	ELECTRIC MEASURING INSTRUMENTS	34	505	
3622	INDUSTRIAL CONTROLS	28	280	
3623	WELDING APPARATUS	11	65	
3632	HOUSEHOLD REFRIGERATORS AND FREEZERS	24	94	
3641	ELECTRIC LAMPS	7	382	
3642	LIGHTING FIXTURES	44	267	
3651	RADIO AND TV RECEIVING SETS	6	12	
3661	TELEPHONE AND TELEGRAPH APPARATUS	13	1,072	
3673	ELECTRON TUBES, TRANSMITTING	14	581	
3679	ELECTRONIC COMPONENTS, NEC	28	148	
3694	ENGINE ELECTRICAL EQUIPMENT	12	2,805	
3711	MOTOR VEHICLES	7	28	

TABLE 2-7. POTENTIAL NICKEL OXIDE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3713	TRUCK AND BUS BODIES	5	5	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	23	133	
3721	AIRCRAFT	26	693	
3722	AIRCRAFT ENGINES AND ENGINE PARTS	5	10	
3742	RAILROAD AND STREET CARS	8	32	
3811	ENGINEERING & SCIENTIFIC INSTRUMENTS	31	80	
3821	MECHANICAL MEASURING DEVICES	57	238	
3851	OPHTHALMIC GOODS	36	383	
3999	MANUFACTURES, NEC	45	90	
4511	CERTIFICATED AIR TRANSPORTATION	5	310	
TOTAL		1,800	51,809	

NATIONAL OCCUPATIONAL EXPOSURE SURVEY (NOES) (1981-1983) (NIOSH, 1990)

CAS #	RTECS #	HAZ	DESCRIPTION
1313-99-1	QR8400000	84269	**NICKEL OXIDE**

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
1743	TERRAZZO, TILE, MARBLE, MOSAIC WORK	317	2,217	
2075	SOYBEAN OIL MILLS	18	321	
2079	SHORTENING AND COOKING OILS	17	51	
2899	CHEMICAL PREPARATIONS, NEC	42	170	
3229	PRESSED AND BLOWN GLASS, NEC	17	1,962	1,660
3312	BLAST FURNACES AND STEEL MILLS	14	1,174	
3315	STEEL WIRE AND RELATED PRODUCTS	33	658	
3429	HARDWARE, NEC	7	13	
3465	AUTOMOTIVE STAMPINGS	3	18	
3612	TRANSFORMERS	44	1,089	87

TABLE 2-7. POTENTIAL NICKEL OXIDE OCCUPATIONAL EXPOSURE ESTIMATES FROM NIOSH SURVEYS (continued)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
3672	CATHODE RAY TELEVISION PICTURE TUBES	2	9	5
3673	ELECTRON TUBES, TRANSMITTING	22	88	44
3674	SEMICONDUCTORS AND RELATED DEVICES	2	67	42
3691	STORAGE BATTERIES	27	485	27
3711	MOTOR VEHICLES AND CAR BODIES	23	2,824	52
3713	TRUCK AND BUS BODIES	3	11	
3714	MOTOR VEHICLE PARTS AND ACCESSORIES	13	65	
3825	INSTRUMENTS TO MEASURE ELECTRICITY	3	1,056	483
3851	OPHTHALMIC GOODS	55	3,861	3,144
3911	JEWELRY, PRECIOUS METAL	12	116	46
4226	SPECIAL WAREHOUSING AND STORAGE, NEC	16	81	
7391	RESEARCH & DEVELOPMENT LABORATORIES	14	1,828	230
TOTAL		702	18,166	5,820

2.5 Regulations and Criteria

EPA regulates nickel compounds under the Clean Air Act (CAA), the Clean Water Act (CWA), the Resource Conservation and Recovery Act (RCRA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Superfund Amendments and Authorization Act (SARA). The nickel salt of an organo compound containing nitrogen is regulated under the Toxic Substances Control Act (TSCA). Effective in 1990, liquid hazardous wastes containing nickel compounds at concentrations $\geq$ 134 mg/L are prohibited from underground injection. Reportable quantities (RQs) have been established for the release of certain nickel compounds. An RQ of 100 lb has been designated for nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate, while a value of 10 lb has been set for nickel carbonyl, nickel cyanide, and nickel hydroxide. Under the Federal Water Pollution Control Act (FWPCA), nickel compounds are designated toxic pollutants. Effluent limitations and pretreatment and performance standards have been created for point sources producing nickel sulfate, nickel chloride, nickel nitrate, nickel fluoborate, and nickel carbonate. FDA regulates the amount of nickel oxide in the color additive chromium-cobalt-aluminum oxide to less than 1%. NIOSH has recommended an exposure limit of 0.007 mg/m^3 as a time-weighted average (TWA; time not specified) for nickel carbonyl and 0.015 mg/m^3 for inorganic nickel compounds (as Ni) in the workplace (NIOSH, 1988; cited by IARC, 1990). NIOSH considers nickel and its compounds to be potential occupational carcinogens and recommends that occupational exposures to carcinogens be limited to the lowest feasible concentration (Ludwig, 1994). OSHA has set a permissible exposure limit (PEL) for nickel carbonyl (as Ni) at 0.007 mg/m^3 as an 8-hour TWA. For other nickel compounds, soluble and insoluble, the PEL is 1 mg/m^3. OSHA also regulates the compounds as hazardous chemicals in laboratories and under the Hazard Communication Standard.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 63—PART 63—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANT FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Code: 42 U.S.C. 7401 et seq.	This part contains national emission standards for hazardous air pollutants (NESHAP) established pursuant to section 112 of the CAA, which regulate specific categories of stationary sources that emit (or have the potential to emit) one or more hazardous air pollutants listed in this part pursuant to section 112(b) of the CAA.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 63—Subpart D—Regulations Governing Compliance Extensions for Early Reductions of Hazardous Air Pollutants.	The provisions of this subpart apply to an owner or operator of an existing source who wishes to obtain a compliance extension from a standard issued under section 112(d) of the CAA. Nickel compounds are listed as high-risk pollutants; the weighting factor is 10.
	40 CFR 63—Subpart JJ—National Emission Standards for Wood Furniture Manufacturing Operations. Promulgated: 60 FR 62936, 12/07/95.	The affected source to which this subpart applies is each facility that is engaged, either in part or in whole, in the manufacture of wood furniture or wood furniture components and that is located at a plant site that is a major source as defined in section 63.2. Nickel subsulfide is listed as a pollutant excluded from use in cleaning and washoff solvents. Nickel carbonyl is listed as a VHAP of potential concern.
	40 CFR 68—PART 68—CHEMICAL ACCIDENT PREVENTION PROVISIONS. Promulgated: 59 FR 4493, 01/31/94. U.S. Code: 42 U.S.C. 7412(r), 7601(a)(1), 7661-7661f.	This part sets forth the list of regulated substances and thresholds, the petition process for adding or deleting substances to the list of regulated substances, the requirements for owners or operators of stationary sources concerning the prevention of accidental releases, and the State accidental release prevention programs approved under section 112(r). Nickel carbonyl is a regulated toxic substance; the threshold quantity for accidental release prevention is 1000 lb. Its toxic endpoint is 0.00067 mg/L.
	40 CFR 116—PART 116—DESIGNATION OF HAZARDOUS SUBSTANCES. Promulgated: 43 FR 10474, 03/13/78. U.S. Code: 33 U.S.C. 1251 et seq.	This regulation designates hazardous substances under section 311(b)(2)(A) of the FWPCA and applies to discharges of substances designated in Table 116.4.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 116.4—Sec. 116.4 Designation of hazardous substances. Promulgated: 43 FR 10474, 03/13/78 through 54 FR 33482, 08/14/89.	Nickel ammonium sulfate, nickel chloride, nickel hydroxide, nickel nitrate, and nickel sulfate are listed as hazardous substances.
	40 CFR 117—PART 117—DETERMINATION OF REPORTABLE QUANTITIES FOR HAZARDOUS SUBSTANCES. Promulgated: 44 FR 50776, 08/29/79. U.S. Code: 33 U.S.C. 1251 et seq.	
	40 CFR 117.3—Sec. 117.3 Determination of reportable quantities. Promulgated: 50 FR 13513, 04/04/85 through 60 FR 30937, 06/12/95.	A reportable quantity of 100 lb (45.4 kg) has been established for nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate, and 10 lb for nickel hydroxide, pursuant to section 311 of the CWA.
	40 CFR 148—PART 148—HAZARDOUS WASTE INJECTION RESTRICTIONS. Promulgated: 53 FR 28154, 07/26/88. U.S. Code: 42 U.S.C. 6901 et seq.	
	40 CFR 148.1—Sec. 148.1 Purpose, scope, and applicability. Promulgated: 61 FR 15596, 04/08/96. Effective 04/08/98.	This part identifies wastes that are restricted from disposal into Class I wells and defines those circumstances under which a waste, otherwise prohibited from injection, may be injected.
	40 CFR 148.12—Sec. 148.12 Waste specific prohibitions—California list wastes. Promulgated: 53 FR 30918, 08/16/88, as amended at 53 FR 41602, 10/24/88.	Liquid hazardous wastes, including free liquids associated with any solid or sludge, containing the nickel and/or nickel compounds at concentrations $\geq$ 134 mg/L are prohibited from underground injection, effective August 8, 1990.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 192—PART 192—HEALTH AND ENVIRONMENTAL PROTECTION STANDARDS FOR URANIUM AND THORIUM MILL TAILINGS. Promulgated: 48 FR 602, 01/05/83. U.S. Code: 42 U.S.C. 2022, as added by the Uranium Mill Tailings Radiation Control Act of 1978.	The provisions of this part control the residual radioactive material at designated processing or depository sites under section 108 of the Uranium Mill Tailings Radiation Control Act of 1978, and applies to the restoration of such sites following any use of the subsurface minerals under section 104(h) of the Uranium Mill Tailings Radiation Control Act of 1978.
	40 CFR 192—Subpart E—Standards for Management of Thorium Byproduct Materials Pursuant to Section 84 of the Atomic Energy Act of 1954, as Amended. Promulgated: 48 FR 45947, 10/07/83.	Nickel and nickel compounds (not otherwise specified), nickel carbonyl, and nickel cyanide are listed as constituents (Appendix I).
	40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTE. Promulgated: 45 FR 33119, 05/19/80. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, 6922, 6924(y), and 6938.	
	40 CFR 261—Subpart D—Lists of Hazardous Wastes, Appendix VIII—Hazardous Constituents. Promulgated: 53 FR 13388, 04/22/88 through 62 FR 32977, 06/17/97. Nickel compounds (not otherwise specified), nickel carbonyl, and nickel cyanide are listed as hazardous constituents.	Appendix VIII is a consolidated list of hazardous constituents identified in this part. Solid wastes containing these constituents are subject to notification requirements of RCRA section 3010 and must be disposed of in RCRA-permitted facilities.
	40 CFR 261.33—Sec. 261.33 Discarded commercial chemical products, off-specification species, container residues, and spill residues thereof. Promulgated: 45 FR 78529 and 78541, 11/25/80.	Nickel carbonyl and nickel cyanide are listed as hazardous waste.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 266—Subpart M—Military Munitions. Promulgated: 62 FR 6654, 02/12/97.	The regulations in this subpart identify when military munitions become a solid waste, and, if these wastes are also hazardous under this subpart or 40 CFR part 261, the management standards that apply to these wastes. The reference air concentration for nickel cyanide is 0 μg/m. The risk specific dose for nickel subsulfide is 2.1×10^{-22} μg/m^3. The residue concentration limit for nickel cyanide is 0.7 mg/kg.
	40 CFR 268—PART 268—LAND DISPOSAL RESTRICTIONS. Promulgated: 51 FR 40638, 11/07/86. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, and 6924.	
	40 CFR 268—Subpart E—Prohibitions on Storage.	Nickel cyanide is a metal-bearing waste prohibited from dilution in a combustion unit according to 40 CFR 268.3 (Appendix XI).
	40 CFR 302—PART 302—DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Code: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	This regulation designates under section 102(a) of the CERCLA those substances in the statutes referred to in section 101(14) of the CERCLA, identifies reportable quantities for these substances, and sets forth the notification requirements for releases of these substances. This regulation also sets forth reportable quantities for hazardous substances designated under section 311(b)(2)(A) of the CWA.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 302.4—Sec. 302.4 Designation of hazardous constituents.	**Compound** — **RQ (lb)** Nickel ammonium sulfate — 100 Nickel carbonyl — 10 Nickel chloride — 100 Nickel cyanide — 10 Nickel hydroxide — 10 Nickel nitrate — 100 Nickel sulfate — 100
	40 CFR 355—PART 355—EMERGENCY PLANNING AND NOTIFICATION. Promulgated: 52 FR 13395, 04/22/87. U.S. Code: 42 U.S.C. 11002, 11004, and 11048.	This regulation establishes the list of extremely hazardous substances, threshold planning quantities, and facility notification responsibilities necessary for the development and implementation of State and local emergency response plans. Nickel carbonyl is listed as an extremely hazardous substance; its threshold planning quantity is 1 lb.
	40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Code: 42 U.S.C. 11023 and 11048.	This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of the SARA of 1986. The information collected under this part is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, to aid in the development of regulations, guidelines, and standards, and for other purposes.
	40 CFR 372.65—Sec. 372.65 Chemicals and chemical categories to which this part applies. Promulgated: 53 FR 4525, 02/16/88; 53 FR 12748, 04/18/88.	The requirements of this subpart apply to nickel compounds—any unique chemical substance that contains nickel as part of that chemical's infrastructure—and became effective on January 1, 1987.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 401—PART 401—GENERAL PROVISIONS. Promulgated: 39 FR 4532, 02/01/74. U.S. Code: 33 U.S.C. 1251, 1311, 1314 (b) and (c), 1316 (b) and (c), 1317 (b) and (c) and 1326(c).	This part sets forth the legal authority and general definitions which will apply to all regulations issued concerning specific classes and categories of point sources under parts 402 through 699 of this subchapter.
	40 CFR 401.15—Sec. 401.15 Toxic pollutants. Promulgated: 44 FR 44502, 07/30/79, as amended at 46 FR 2266, 01/08/81; 46 FR 10724, 02/04/81.	Nickel compounds are toxic pollutants designated pursuant to section 307(a)(1) of the FWPCA.
	40 CFR 415—PART 415—INORGANIC CHEMICALS MANUFACTURING POINT SOURCE CATEGORY. Promulgated: 47 FR 28278, 06/29/82. U.S. Code: 33 U.S.C. 1311, 1314 (b), (c), (e), and (g), 1316 (b) and (c), 1317 (b) and (c), and 1361.	
	40 CFR 415—Subpart A—Aluminum Chloride Production Subcategory.	
	40 CFR 415.1—Sec. 415.1 Compliance dates for pretreatment standards for existing sources. Promulgated: 49 FR 33420, 08/22/84; 49 FR 37594, 09/25/84.	The compliance date for discharges from nickel sulfate manufacturing operations and for all subparts in part 415 not listed in paragraphs (a) and (b) of this section is June 29, 1985.
	40 CFR 415—Subpart AU—Nickel Salts Production Subcategory. Promulgated: 49 FR 33423, 08/22/84.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	40 CFR 415.470—Sec. 415.470 Applicability; description of the nickel salts production subcategory.	This subpart is applicable to discharges and to the introduction of pollutants into treatment works which are publicly owned resulting from the production of nickel salts, including nickel sulfate, nickel chloride, nickel nitrate, nickel fluoborate, and nickel carbonate.
E P A	40 CFR 415.472—Sec. 415.472 Effluent limitations guidelines representing the degree of effluent reduction attainable by the application of the best practicable control technology currently available (BPT).	Except as provided in 40 CFR 125.30 through 125.32, for any existing point source producing nickel sulfate, nickel chloride, nickel nitrate, or nickel fluoborate, the limits for total nickel are 0.0060 kg/kkg (1-day maximum) and 0.0020 kg/kkg (30-day avg.). For a source producing nickel carbonate, the limits for total nickel are 1.1 kg/kkg (1-day maximum) and 0.35 kg/kkg (30-day avg.).
	40 CFR 415.473—Sec. 415.473 Effluent limitations guidelines representing the degree of effluent reduction attainable by the application of the best available technology economically achievable (BAT).	Except as provided in 40 CFR 125.30 through 125.32, for any existing point source producing nickel sulfate, nickel chloride, nickel nitrate, or nickel fluoborate, the limits for total nickel are 0.00074 kg/kkg (1-day maximum) and 0.00024 kg/kkg (30-day avg.). For a source producing nickel carbonate, the limits for total nickel are 0.13 kg/kkg (1-day maximum) and 0.042 kg/kkg (30-day avg.).

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	40 CFR 415.474—Sec. 415.474 Pretreatment standards for existing sources (PSES).	Except as provided in 40 CFR 403.7 and 403.13, for any existing source producing nickel sulfate, nickel chloride, nickel nitrate, nickel fluoborate, or nickel carbonate which introduces pollutants into a POTW, the limits for total nickel are 1.1 kg/kkg (1-day maximum) and 0.36 kg/kkg (30-day avg.). In cases where POTWs find it necessary to impose mass limitations, the limits for total nickel are the same as specified in 415.473.
E P A	40 CFR 415.475—Sec. 415.475 New source performance standards (NSPS).	For any new source subject to this subpart and producing nickel sulfate, nickel chloride, nickel nitrate, or nickel fluorobate, the limits for total nickel are 0.00074 kg/kkg (1-day maximum) and 0.00024 kg/kkg (30-day avg.). For any new source producing nickel carbonate, the limits for total nickel are 0.13 kg/kkg (1-day maximum) and 0.042 kg/kkg (30-day avg.).
	40 CFR 415.476—Sec. 415.476 Pretreatment standards for new sources (PSNS).	Except as provided in 40 CFR 403.7, for any new source subject to this subpart and producing nickel sulfate, nickel chloride, nickel nitrate, nickel fluoborate, or nickel carbonate which introduces pollutants into a POTW, the limits for total nickel are the same as specified in 415. 474.
	40 CFR 455—PART 455—PESTICIDE CHEMICALS. Promulgated: 43 FR 17776, 04/25/78. U.S. Code: 33 U.S.C. 1311, 1314, 1316, 1317, and 1361.	The appropriate pollution control technology for nickel sulfate hexahydrate is given in Table 10.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	40 CFR 721—PART 721—SIGNIFICANT NEW USES OF CHEMICAL SUBSTANCES. Promulgated: 53 FR 28359, 07/21/88. U.S. Code: 15 U.S.C. 2604, 2607, and 2625(c). 40 CFR 721—Subpart E—Significant New Uses for Specific Chemical Substances.	
EPA	40 CFR 721.5330—Sec. 721.5330 Nickel salt of an organo compound containing nitrogen. Promulgated: 58 FR 51685, 11/04/93.	The chemical substance generically identified as nickel salt of an organo compound containing nitrogen is subject to reporting under this section for the following significant new uses: protection in the workplace; hazard communication program; industrial, commercial, and consumer activities; disposal; and release to water.
FDA	21 CFR 73—PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION. Promulgated: 42 FR 15643, 03/22/77. U.S. Code: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, and 379e. 21 CFR 73—Subpart B—Drugs. 21 CFR 73.1015—Sec. 73.1015 Chromium-cobalt-aluminum oxide. Promulgated: 42 FR 15643, 03/22/77, as amended at 49 FR 10089, 03/19/84.	The color additive chromium-cobalt-aluminum oxide may contain small amounts (less than 1%) of nickel oxide.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
O S H A	29 CFR 1910—PART 1910—OCCUPATIONAL SAFETY AND HEALTH STANDARDS. Promulgated: 39 FR 23502, 06/27/74.	
	29 CFR 1910—Subpart H—Hazardous Materials. U.S. Code: 29 U.S.C. 653, 655, 657.	
	29 CFR 1910.119—Sec. 1910.119 Process safety management of highly hazardous chemicals.	Nickel carbonyl is listed as a toxic and highly reactive hazardous chemical which presents a potential for a catastrophic event at or above the threshold quantity.
O S H A	29 CFR 1910—Subpart Z—Toxic and Hazardous Substances. Promulgated: 39 FR 23502, 07/27/74. Redesignated: 40 FR 23072, 05/28/75. U.S. Code: 29 U.S.C. 653, 655, and 657.	Regulation provides for protective clothing and hygiene requirements for workers, open vessel operations restricted, engineering requirements, respirators, medical surveillance requirements for workers, exhaust fan requirements, sign requirements for regulated areas, and labeling requirements for containers.
	29 CFR 1910.1000—Sec. 1910.1000 Air contaminants. Promulgated: 58 FR 35340, 06/30/93 through 62 FR 1600, 01/10/97.	PEL for nickel carbonyl (as Ni) $\leq$ 0.007 mg/m^3, as an 8-hr TWA. PEL for nickel insoluble and soluble compounds (as Ni) $\leq$ 1 mg/m^3, as an 8-hr TWA.
	29 CFR 1910.1200—Sec. 1910.1200. Hazard Communication. Promulgated: 61 FR 9245, 03/07/96. U.S. Code: also includes 5 U.S.C. 553.	Requires chemical manufacturers and importers and all employers to assess chemical hazards and to provide information to employees. Hazard Communication Program to include labels, materials safety data sheets, and worker training.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
	29 CFR 1910.1450—Sec 1910.1450. Occupational exposure to hazardous chemicals in laboratories. Promulgated: 55 FR 3327, 01/31/90 through 55 FR 12111, 03/30/90.	As select carcinogens (IARC group 1 and NTP known carcinogens), nickel compounds are included as a chemical hazard in laboratories. Employers are required to provide employee information and training and a Chemical Hygiene Plan.
	29 CFR 1915—PART 1915—OCCUPATIONAL SAFETY AND HEALTH STANDARDS FOR SHIPYARD EMPLOYMENT. Promulgated: 47 FR 16986, 04/20/82. U.S. Code: 29 U.S.C. 653, 655, and 657.	
	29 CFR 1915—Subpart Z—Toxic and Hazardous Substances. Promulgated: 58 FR 35514, 07/01/93.	

OSHA	29 CFR 1915.1000—Sec. 1915.1000 Air contaminants. Promulgated: 61 FR 31430, 06/20/96.	The requirements applicable to shipyard employment under this section are identical to those set forth in section 1910.1000.
	29 CFR 1926—PART 1926—SAFETY AND HEALTH REGULATIONS FOR CONSTRUCTION. Promulgated: 44 FR 8577, 02/09/79; 44 FR 20940, 04/06/79.	
	29 CFR 1926—Subpart D—Occupational Health and Environmental Controls.	
	29 CFR 1926.55—Sec. 1926.55 Gases, vapors, fumes, dusts, and mists. Promulgated: 39 FR 22801, 06/24/74 through 62 FR 1619, 01/10/97.	The requirements applicable to construction employment under this section are identical to those set forth in section 1910.1000.

[a]The regulations in this table have been updated through the following 1998 Code of Federal Regulations: 21, 19, and 40 in February 1999.

3.0 HUMAN STUDIES

3.1 Review of Nickel Compound Epidemiology (IARC, 1990, and ICNCM, 1990)

The IARC Working Group for consideration of nickel and nickel compounds concluded nickel compounds are carcinogenic to humans. The reviewed studies evaluated the risk from occupational exposure to nickel and nickel compounds. There is sufficient evidence for the carcinogenicity of nickel sulfate in humans, and of combinations of nickel sulfides and oxides encountered in the nickel refining industry. Carcinogenicity of the respiratory tract is the main chronic effect reported in relation to nickel and its compounds. The risks were highest for lung and nasal cancers among calcining workers who were heavily exposed to sulfidic, oxidic, and metallic nickel.

The separate effects of oxides and sulfides could not be estimated as high exposure was always either to both, or to oxides together with soluble nickel. In addition, the presence of many potential confounders (sulfuric acid mists, oxide and sulfide ores other than nickel, and smoking) increased the difficulty in identifying the causative agent(s). Also, an increased cancer incidence was reported only in workers employed prior to 1955, when exposure levels were estimated to be 1-10 mg Ni/m^3 (consisting mainly of Ni-Cu oxides). Since 1955, levels are estimated to be between 1-5 mg Ni/m^3 (consisting mainly of impure NiO).

A comprehensive review of the epidemiological studies of cancer and human exposure to nickel was also performed in 1990 by the International Committee on Nickel Carcinogenesis in Man (ICNCM, see Appendix A). This review, including a recent analysis of one case-control study and nine cohort studies, concludes that cancers of the lung and nasal cavities are significantly higher in nickel refinery workers than the general population (Steenland et al., 1996). However, causal relationships between cancer and nickel exposure in U.S. refineries are confounded by other factors.

Mortality studies of exposed workers in the nickel alloy industry demonstrate no consistent association with lung cancer. The few studies reporting positive results could not separate the cancer risk associated with nickel from other confounding factors, such as exposure to known carcinogens like chromium (Steenland et al., 1996). According to the ICNCM report, when operations at the Riddle, Oregon, refinery were in progress, analysis of the epidemiological data for the refinery found only a modest excess of lung cancer mortality. No malignancies of the nasal passages or sinuses, and no significant excess of any other type of cancer were reported (ICNCM, 1990). The excess in the incidence of lung cancers was found in a subgroup of short-term workers exposed for less than one year, whereas workers with chronic exposure had no significant excess in mortality due to lung cancer. In contrast, workers in Canadian and European refineries, which process sulfidic ores, had increased incidences of respiratory cancer (ICNCM, 1990).

3.2 Studies Post-IARC (1990)

Full design details and results for the studies described in this section are presented in **Table 3-1**. To facilitate comparison, Standardized Mortality Ratios (SMRs), Odds Ratios (ORs), and Relative Risk Ratios (RRs) reported in this section have all been converted to base 1.

3.2.1 Metallic Nickel

Two studies (published without information regarding levels of nickel exposure) of stainless steel and ferrochromium production workers and welders in France found no significant excess risk of lung cancer. The first study involved a cohort of 2269 men followed from 1952 to 1982 (Moulin et al., 1990). Stainless steel production began in 1958. Causes of death were obtained from general practitioners or hospital records. The SMR for lung cancer was not statistically raised in the overall cohort (SMR = 1.40, 95% CI = 0.72-2.45). The higher rate of lung cancer (SMR = 2.04, 95% CI = 1.02-3.64) seen in workers exposed for at least one year in workshops producing stainless steel or ferrochromium could have been due to confounding exposures to polycyclic aromatic hydrocarbons (PAHs).

The second study (Moulin et al., 1993) examined welders in French factories. The cohort consisted of 2721 welders, and mortality was followed from 1975 to 1988. There was no significant excess of lung cancer in all welders compared to controls, but the lung cancer incidence was increased in mild steel welders compared to other subgroups of welders. The lung cancer mortality among mild steel welders was also significantly increased with an exposure duration and latency period of $\geq$ 20 years.

3.2.2 Nickel Carbonyl

The only epidemiological study specifically investigating the possible carcinogenic effect of nickel carbonyl provided no conclusive results. The study focused on 69 men who died between 1933 and 1966 in Wales whose work history included absence from the refinery due to accidental exposure to nickel carbonyl. Their SMR for lung cancer was not statistically significant at 1.52 (95% CI = 0.56-3.31) (Morgan, 1992).

3.2.3 Oxidic Nickel

A European study of 11,092 welders that compared the mortality experiences of shipyard welders, mild steel welders, and those who had ever welded stainless steel provided no definitive evidence of increasing cancer mortality with higher cumulative exposure to nickel (Simonato et al., 1991), although the SMR for all malignant neoplasms for the overall cohort was significantly increased at 1.13 (95% CI = 1.00-1.26). There were no carcinomas of the nose or nasal cavities. The SMR for carcinoma of the trachea, bronchus, and lung was 1.34 (95% CI = 1.10-1.60).

Stainless steel welders would have been exposed to a much higher level of nickel and chromium than those welding mild steel. The lung cancer SMR for mild steel welders was 1.78 (95% C I= 1.27-2.43), 1.28 (95% CI = 0.91-1.75) for those who ever welded stainless steel, and 1.23 (95% CI = 0.75-1.90) for those who predominantly welded stainless steel. Within this last group, there was a non-significant increase in lung cancer SMR with duration of employment: <9 years, SMR = 0.98 (95% CI = 0.40-2.02); >10 years, SMR=1.43 (95% CI = 0.76-2.44). There was no information on the smoking habits or the previous occupational exposure of the cohort (Simonato et al., 1991).

3.2.4 Soluble Nickel

A cohort study of 418 (369 male and 49 female) workers employed at a Finnish nickel refinery (1960-1987) reported a two-fold increased incidence of lung cancer (CI = 0.3-7.4) and a large increase for sinonasal cancer (SIR = 53.8; CI = 1.4-300), however, these estimates were based on only 2 and 1 observed cases, respectively (Karjalainen et al., 1992). The small size of the study and follow-up period limit the conclusions that can be drawn.

Exposures in the refinery were principally to soluble nickel compounds, mainly nickel sulfate, and to a lesser extent, nickel chloride. No nickel oxides were reported to be present, although low levels (between 0.05 and 0.2 mg Ni/m^3) of nickel subsulfide and nickel hydroxide (levels not reported) were noted to be present in certain areas of the refinery. Overall, average levels of nickel ranged between 0.1-0.5 mg Ni/m^3. Copper/nickel smelter workers and maintenance workers were followed from 1953-1987 and nickel refinery workers from 1960-1987. There were ten cases of lung cancer observed while 9.2 were expected. In the original follow-up period, there was one case of sinonasal cancer, but two further cases of sinonasal cancer were diagnosed after the closing date of follow-up.

Exposure to sulfuric acid (and allied) mists has been associated with increased risk of various respiratory cancers and is identified as a possible confounder in this study. The workers in this study showed no significant increase in standard incidence rates (SIR) of non-respiratory cancer.

A follow-up to this study reports an updated analysis of cancer incidence among the Finnish worker cohort (Anttila et al., 1998). A total of 1,155 workers were presumed to have potential nickel exposure based upon dates of employment (after January 1, 1960 which corresponds to the start of nickel smelting and refining). The vital status of nearly all cohort members (99.4%) was determined. Linkage with the national cancer registry of Finland ascertained incident cases of cancer among the cohort. Follow-up was extended from the end of 1987 to December 31, 1995. An elevated risk of nasal cancer was found among refinery workers (SIR = 41.1; CI = 4.9- 148) with a greater increased risk among workers with a longer latency (20+ years; SIR = 67.1) and duration of employment (5+ years; SIR = 75.2). An increased risk of lung cancer was also found for nickel refinery workers (latency of 20+ years SIR = 3.4).

The additional follow-up provided a relatively complete latency period, although the size of the cohort limits the precision of many risk estimates. For example, the association with nasal cancer is quite suggestive, but is based upon only 2 cases among the exposed nickel workers. Other aspects of the study design are strengths such as the excellent tracing and linkage with a national cancer registry. The potential confounding effects of other workplace and exposures is of concern. Examination of the risk estimates for the unexposed (to nickel) cohort shows a 1.5-fold increased risk for lung cancer raising the possibility that some of the excess risk attributed to nickel exposure may be due to other factors.

Another European study (Andersen et al., 1996) suggests an association between work in a nickel refinery and an increased incidence of cancers. This cohort cancer incidence study of 4764 Norwegian nickel refinery workers found an elevated incidence for nose and nasal cavity cancer (SIR = 18.0; CI = 12.3-25.4) and lung cancer (SIR = 3.0; CI = 2.6-3.4). A moderately increased risk of laryngeal cancer was also found (SIR = 1.6; CI = 0.8- 2.8). An analysis of nickel

compounds showed a dose-response gradient for lung cancer with cumulative exposure to soluble nickel after adjustment for nickel oxide, smoking, and age, in addition to a multiplicative interaction between smoking and total nickel exposure.

3.3 Other Occupational Exposure Studies

The largest body of epidemiological data linking increased incidences of cancer and nickel exposures is from the European and Canadian communities, where the source of nickel is mainly from copper-sulfidic nickel ores. Exposures were mainly to the more dust-generating nickel processes, and those primarily occurring prior to the 1930's. No recent epidemiologic data exists for U.S. nickel refinery workers, who were mainly exposed to either lateritic ores (oxides or silicates, with much lower copper content than European varieties), or to garnierite (a complex nickel magnesium silicate associated with iron, cobalt, chromium, and aluminum, and containing about 0.5 percent cobalt) (Carson, 1980). Since the possible contribution of copper to potential carcinogenicity has not been extensively investigated, caution may be needed when making comparisons between U.S. and non-U.S. studies.

One European study which might be relevant to the United States is an update to an earlier study of French refinery workers in New Caledonia, using lateritic ores similar to those used in U.S. processes (Goldberg et al., 1994). The study did not find an increased incidence of respiratory and upper aerodigestive tract cancers among male nickel workers compared with the incidence among the general male population of New Caledonia for a ten-year period (1978-1987). Further, there was no increased incidence of these cancers when stratified by duration of exposure. A nested case-control study using a job-exposure matrix to classify workers according to 20 specific exposure groups did not show a pattern of association with lung, larynx, or pharynx cancer for nickel-related exposures. Many of the risk estimates for the exposure-based analysis were imprecise with wide confidence intervals.

Recent studies in the United States which suggest an association between occupational nickel exposure and cancer, like their European counterparts, cannot attribute the increased incidence of cancer to any one specific form of nickel. Additionally, none of the studies examined U.S. refinery workers specifically. Two of the studies (Wortley et al., 1992; Horn-Ross et al., 1997), while conducted in the United States, did not specify the type of nickel exposure, nor even the industry. A link between laryngeal cancer and occupational exposure to nickel ($n = 235$; $RR = 1.6$; $CI = 0.4\text{-}6.7$) was reported in a study of cases in the western Washington region (Wortley et al., 1992). In this analysis, patients were assigned numerical risk ratings, based upon self-reported occupations and the potential risk of nickel exposure; comparisons were made between the incidence of laryngeal cancer and exposure scores.

Another study (Horn-Ross et al., 1997) of patients diagnosed with cancer of the salivary glands found a substantial dose-dependent association between cumulative hours of worker exposure to nickel compounds or alloys and an increased risk of cancer of the salivary glands. A major criticism of the study, aside from the small number of patients in the "high" risk group, is the potential misclassification of nickel exposure using job title and a job-exposure matrix. In addition, neither of these studies attempted to qualify the type of nickel exposure, combining all nickel compounds and alloys into one group.

Some of the more recent studies suggesting a link between incidence of cancer and nickel exposure (Karjalainen et al., 1992; Wortley et al., 1992; Horn-Ross et al., 1997) are limited by the relatively small number of subjects studied. In addition, exposure to nickel was largely self-reported, and potential exposure to other potential carcinogens (e.g., mists of sulfuric acid) were not taken into account in some studies. The recent study by Anderson et al (1996) does suggest an association between nickel exposure, in particular soluble nickel, and an increased risk of lung and nasal cancer. The risk estimate for lung cancer was relatively precise and the study did account for smoking and utilized cumulative exposure measures based upon available direct measurements of nickel concentrations.

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Cohort	2,269 male stainless steel and ferrochromium production workers in France followed from 1952 to 1982	Metallic nickel no data regarding levels of nickel exposure.	Significant excess in lung cancer; SMR for workers exposed for ≥ 1 yr in stainless steel or ferrochromium shops = 2.04, 95% CI = 1.02-3.64.	Nested case-control study of lung cancer cases showed elevated OR for welders exposed only to nickel and/or chromium and not PAHs (OR = 3.4; CI= 0.4-32.4). Smoking similar in exposed and non-exposed groups		Moulin et al. (1990)
Cohort	69 male refinery workers who died between 1933 and 1966	Nickel carbonyl effects of accidental exposure caused work absences in this cohort	Lung cancer SMR not significant at 1.52			Morgan (1992)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Reference
Cohort	11,092 welders (shipyard, mild steel, stainless steel) from 135 companies in nine European countries	Oxidic nickel Stainless steel workers would have been exposed to a much higher level of nickel and chromium than those welding mild steel.	SMR for all malignant neoplasms for the overall cohort was significantly increased at 1.13 (95% CI = 1.00-1.26). The SMR for carcinoma of the trachea, bronchus, and lung was 1.34 (95% CI = 1.10-1.60). SMRs (95% CI) Mild steel = 1.78 (1.27-2.43) Stainless steel (ever) = 1.28 (0.91-1.75) Stainless steel (predominantly) = 1.23 (0.75-1.90)	No data on smoking habits or previous occupational exposure of cohort.	Simonato et al. (1991)
Cohort	2,721 welders in 13 factories in France; internal comparison group of 6,683 manual workers; mortality determined 1975-1988	Oxidic nickel no data on levels of exposure to nickel	No significant excess of lung cancer in all welders compared to controls; increased lung cancer in mild steel welders compared to stainless steel welders Overall SMR for lung cancer in all welders = 1.24, 95% CI = 0.75-1.94. Stainless steel welders (SMR = 1.1; 95% CI = 0.4-2.6); non-shipyard mild steel welders (SMR=1.59, 95% CI = 0.73-3.02) and significant increase for $\geq$ 20 yr duration and latency	Smoking; no significant difference between exposed and non-exposed groups	Moulin et al. (1993)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Cohort	418 workers (369 M, 49 W) in a Finnish nickel refinery after 1960; cancer incidence followed up from 1960-1987.	Soluble nickel Measured levels of 0.1-0.5 mg/m^3 from personal sampling in the 1970s; 1.1 mg Ni/m^3 highest recorded single concentration in electrowinning dept.; urine conc. < 0.85 :mol/L in leaching workers and 1.5-2 :mol/L in electrowinning workers	Calculated standardized incidence ratios (SIRs): Sinonasal cancer SIR (95% CI; no. obsd/no. exp) 53.8 (1.4-300. 1/0.018) Stomach cancer SIR (95% CI; no. obsd/no. exp) 4.3 (0.5-16; not given) Lung cancer SIR (95% CI; no. obsd/no. exp) 2.0 (0.3-7.4; 2/1)	Effects of smoking could not be evaluated due to lack of historical information.	Overall cancer risk among workers exposed to nickel was the same as in the reference population. Increased incidence of lung and nasal cancers indicates that even moderate or low nickel exposures can be hazardous.	Karjalainen et al. (1992)
Cohort	418 workers (369 M, 49 W) in a Finnish nickel refinery continuously employed at least 3 mo 1945-1985; cancer incidence followed up through 1995.	Soluble nickel Measured levels of 0.2-0.8 mg/m^3 from stationary samplers 1967-1988; 0.1-0.4 mg /m^3 in breathing zone samples taken 1979-1981; 1.2 mg /m^3 highest recorded single concentration measured at stationary sites in electrowinning work area; most exposure to Ni sulfate after 1973	Calculated standardized incidence ratios (SIRs): Sinonasal cancer SIR (95% CI; no. obsd/no. exp) 41.1 (4.97-148; 2/0.05) Stomach cancer SIR (95% CI; no. obsd/no. exp) 4.98 (1.62-11.6; 5/1.0) Lung cancer SIR (95% CI; no. obsd/no. exp) 2.61 (0.96-5.67; 6/2.3)	Effects of smoking could not be evaluated due to lack of historical information.	Overall cancer risk among workers exposed to nickel was the same as in the reference population. Increased incidence of lung and nasal cancers indicates that even moderate or low nickel exposures can be hazardous.	Anttila et al. (1998)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Cohort	4,764 nickel refinery workers; 379 workers with first employment 1916-1940, with at least 3 yr of employment, and 4,385 workers with at least 1 yr of employment 1946-83.	Soluble nickel Measurement of atmospheric nickel in most process areas in 1973; few measurements in 1952-1953 and 1964 Concentrations of total airborne nickel and different forms estimated by experts (engineers, medical personnel, others with refinery experience) Assumed that nickel species occurred in respirable dust in same proportion as in material handled in work areas; species divided into four categories: metallic, oxidic, soluble, sulfidic	Two analyses: 1) SIR 2) Poisson regression for RR SIR (95% CI; no. obsd/no. exp.) 18 (12-25; 32/1.8) for nasal cancer 3 (2.6-3.4; 203/68) for lung cancer RR (95% CI) of lung cancer 1.1 (0.2-5.1) for exposed workers (never smoked): 5.1 (1.3-20.5) for exposed workers (smoked) *Soluble nickel:* Mean Exposure mg/m^3, (n) — RR — 95% CI 0.1 (86) — 1.0 — referent 2.3 (36) — 1.2 — (0.8-1.9) 8.8 (23) — 1.6 — (1.0-2.8) 28.9 (55) — 3.1 — (2.1-4.8) *Nickel oxide:* Mean Exposure mg/m^3, (n) — RR — 95% CI 0.4 (53) — 1.0 — referent 2.5 (49) — 1.0 — (0.6-1.5) 8.3 (53) — 1.6 — (1.0-2.5) 44.3 (45) — 1.5 — (1.0-2.2)	RR adjusted for smoking, age; RRs for soluble nickel and nickel oxide adjusted for each other		Andersen et al. (1996)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Case-control nested in nickel workers cohort	Cases: 112 male workers at a New Caledonia, France nickel refinery; all cases of cancer were diagnosed between 1978 and 1987, and each had worked at the company >10 yr. Controls: 298 non-exposed males from the general population in New Caledonia.	Established a job-exposure matrix for various categories of nickel compounds and agents considered to be potential confounders; levels of exposure evaluated by industrial hygienists based on measurements and chemical analyses	Calculated age-adjusted ORs and 95% CI for cumulative exposure and total duration of exposure (considering latency and lag periods); no significant increase in respiratory cancer risk, including pleural, upper respiratory tract, and nasal cancers.	Alcohol and tobacco consumption reported for 3-yr period (1978-81), no change in ORs adjusted for these factors		Goldberg et al. (1994)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Case-control	Cases: 235 patients diagnosed with laryngeal cancer between Sept. 1983 and Feb. 1987 in western Washington area. Controls: 547 men and women, identified by random-digit dialing.	Personal interviews to obtain lifetime occupational histories; prepared a job exposure matrix that included potential nickel exposure; no actual measurements	Odds ratios and 95% CI were for laryngeal cancer estimated using unconditional logistic regression analyses, controlling for alcohol use, cigarette smoking, age and education. Suggestion of increased risk of laryngeal cancer with exposure scores of ≥ 20 Odds Ratio (95% CI): 1.6 (0.4-6.7)	Chromium exposure, age, alcohol use, education, smoking	Strengths: use of a population-based design for the ID of cases and controls, adjusted for smoking, alcohol use, major risk factors for laryngeal cancer; analyses based on latency, peak, duration and intensity of exposure. Weaknesses: potential misclassifica-tion of nickel exposure using job title, a job-exposure matrix, and a small number of subjects	Wortley et al. (1992)

Table 3-1. Studies of Human Exposure to Nickel Published Post-IARC (1990) (Continued)

Design	Population Groups	Exposure	Effects	Potential Confounders	Comments	Reference
Case-control	Cases: 141 men and women diagnosed with salivary gland tumors in one area of California Controls: 191 men and women, identified by random-digit dialing, and from the Health Care Finance Administration Files; frequency-matched to cases by 5-yr age group and sex	Self-reported occupational exposure from telephone interviews.	Odds ratios and 95% CI were estimated using unconditional logistic regression analyses, controlling for age and sex. Odds Ratio (95% CI): 6.0 (1.6-22.0) for ever-exposed 3.7 (0.71-19.8) for lifetime exposure > 3,000 hr 9.0 (1.1-77.2) for lifetime exposure ≤ 3,000 hr	Age, sex	Exposure to Ni compounds & alloys associated with a substantial risk, evidence of a dose-response relation for cumulative hrs of exposure.	Horn-Ross et al. (1997)

adj. = adjusted; exp = expected; obsd = observed

4.0 EXPERIMENTAL CARCINOGENESIS

4.1 Studies Reviewed in IARC (1990)

IARC (1990) found sufficient evidence for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides, and crystalline nickel sulfides in experimental animals. Numerous studies confirm the carcinogenic potential of these compounds at various sites in rodents. IARC found limited evidence in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonides, nickel selenides, and nickel telluride. There was not adequate evidence for the carcinogenicity of nickel trioxide, amorphous nickel sulfide, and nickel titanate in experimental animals.

4.2 Animal Carcinogenicity Studies Post-IARC (1990)

4.2.1 NTP (1996) Studies of Nickel Oxide, Nickel Sulfate Hexahydrate, and Nickel Subsulfide

The National Toxicology Program (NTP) selected nickel oxide and nickel sulfate hexahydrate, compounds commonly found in the workplace in the United States, and nickel subsulfide, linked by an earlier study to lung cancer in rats, for chronic inhalation two-year studies in $B6C3F_1$ mice and F344/N rats (NTP, 1996a, b, and c).

Rats were exposed to nickel oxide concentrations of 0, 0.62, 1.25, or 2.5 mg/m^3 for six hours per day, five days per week for 104 week. Mice were exposed to nickel oxide concentrations of 0, 1.25, 2.5, or 5 mg/m^3 for six hours per day, five days per week for 104 weeks. The results indicated significantly ($p< 0.05$) increased rates of alveolar/bronchiolar adenoma or carcinoma (combined) for male and female rats in 1.25 and 2.5 mg/m^3 exposure groups. An increased incidence of benign pheochromocytoma of the adrenal medulla was observed in both sexes, but an increase in malignant pheochromocytomas was observed only in males. This study did not find that nickel oxide was carcinogenic in male mice, but found some evidence of carcinogenic activity in female mice based on increased incidence of alveolar/bronchiolar adenoma in the 2.5 mg/m^3 exposure group, and increased incidence of alveolar/bronchiolar adenoma or carcinoma in the 1.25 mg/m^3 exposure group.

Rats were exposed to nickel sulfate hexahydrate concentrations of 0, 0.12, 0.25, or 0.5 mg/m^3 for six hours per day, five days per week for 104 weeks. Mice were exposed to nickel sulfate hexahydrate concentrations of 0, 0.25, 0.5, or 1 mg/m^3 for six hours per day, five days per week for 104 weeks. Results did not indicate that nickel sulfate hexahydrate was carcinogenic in rats or mice.

Rats were exposed to nickel subsulfide concentrations of 0, 0.15, or 1 mg/m^3 for six hours, five days per week for 104 weeks. Mice were exposed to nickel subsulfide concentrations of 0, 0.6, or 1.2 mg/m^3 for six hours, five days per week for 105 weeks. Nickel subsulfide caused exposure-related increases in the incidence of alveolar/bronchiolar adenomas, alveolar/ bronchiolar carcinoma, alveolar/bronchiolar adenoma or carcinoma. In addition, benign and malignant pheochromocytomas of the adrenal medulla were significantly increased in male rats. With the exception of malignant pheochromocytomas, similar effects were seen in the female rats (NTP, 1996a, b, and c). Nickel subsulfide was not shown to be carcinogenic in mice.

4.2.2 Nickel Subsulfide

In a study of the effect of local inflammation on nickel subsulfide carcinogenesis in male F344/NCr rats, *Mycobacterium bovis* (MB) injected at the same injection site as nickel subsulfide inhibited localized tumor development (Kasprzak and Ward, 1991). The prevention of nickel sulfide tumors by local MB might result from the localization of numerous natural killer (NK) cells and macrophages and the formation of giant cells observed at the injection site of nickel subsulfide 1-14 days post injection. Presumably, enhanced macrophage activity would cause increased solubilization of the insoluble nickel subsulfide and thereby enhance tumor response. However, the results of the experiment showed that augmentation of the inflammatory response at the site of nickel subsulfide injection was followed by the nearly complete prevention of nickel-induced muscle tumor development (Kasprzak and Ward, 1991). Treatment with anti-inflammatory agents, which would hypothetically reduce solubilization of the nickel and thus reduce tumor formation, had no significant effect on nickel subsulfide tumor incidence, but actually shortened the latency of tumors as compared to treatment with nickel subsulfide alone.

In another investigation, magnesium basic carbonate (MgCarb) was an antagonist and metallic iron powder was a promoter of nickel carcinogenesis in rat kidney (Kasprzak et al., 1994). F344/NCr rats were injected in the renal cortex of each pole of the right kidney with either nickel subsulfide alone or with equimolar doses of MgCarb or metallic iron powder. The results showed that MgCarb inhibited and iron enhanced nickel carcinogenesis. Previous experimentation with the skeletal muscles of F344/NCr rats showed that both MgCarb and iron suppressed nickel subsulfide carcinogenicity, apparently by affecting local inflammatory/phagocytic response towards nickel subsulfide particles (Kasprzak et al., 1987; Kasprzak and Rodriguez, 1992; both cited by Kasprzak et al., 1994). Within the kidney, magnesium seemed to attenuate the uptake of nickel subsulfide by macrophages and tubular epithelial cells, as it did in skeletal muscle, while iron tended to enhance that uptake. No clear reason for the difference in activity of iron in the skeletal muscles versus the kidneys of rats was identified.

An investigation of the genetic factors involved in nickel carcinogenicity versus toxicity demonstrated a reverse order of susceptibility in three strains of male mice dosed with nickel subsulfide (Rodriguez et al., 1996). C57BL, C3H, and $B6C3F_1$ mice were injected with a single dose of nickel subsulfide at concentrations of 0, 0.5, 1.0, 2.5, 5.0, or 10.0 mg in the thigh muscle and observed for up to 78 weeks. The final incidence of local sarcomas in the 5 mg nickel subsulfide dose groups was C3H (97%)> $B6C3F_1$ (76%) > C57BL (40%). C3H mice developed more injection site tumors with a shorter latency period than mice of the other two strains. The results of this experiment suggest that the acute toxicity and carcinogenicity of nickel subsulfide and nickel subsulfide-derived soluble nickel(II) in mice depends on genetic background.

4.2.3 Nickel Acetate

Soluble nickel(II) acetate tetrahydrate was an effective initiator of renal cortical epithelial tumors at a dose of 90 μmol/kg body weight administered by single intraperitoneal (i.p.) injection to male F344/NCr rats at 5 weeks of age (Kasprzak et al., 1990). Renal cortical epithelial tumors

occurred after dosing with sodium barbital, a known renal tumor promoter. One rat given the nickel injection without the promoter developed a single renal cortical adenoma, while multiple tumors, some of which were metastatic to the lung, liver, and spleen, were common in rats given nickel and barbital. These results indicate that soluble nickel is an effective initiator of the carcinogenic process.

Diwan et al. (1992) investigated the transplacental carcinogenic effects of nickel(II) acetate in rats. Two groups of 24 F344/NCr rats were given nickel(II) acetate i.p. Group 1 received 90 μmol/kg body weight once a day on day 17 of gestation. Group 2 received 45 μmol/kg body weight/day twice on gestation days 16 and 18. Offspring were divided into four groups (1A, 1B, 2A, 2B). The A groups received tap water while the B groups received drinking water containing 500 ppm sodium barbital during weeks 4-85 of age. Malignant pituitary tumors occurred in rats given nickel(II) acetate with or without the barbital promoter, and pituitary tumor incidence was elevated in both sexes given nickel(II) acetate prenatally. These pituitary tumors induced with nickel were malignant, in marked contrast to the benign nature of most spontaneous pituitary tumors in rats. The male rats given nickel and barbital developed renal cortical epithelial and renal pelvic transitional epithelial tumors. No renal tumors occurred in female rats or in rats given nickel(II) acetate only. This study provided evidence that the soluble nickel compound, nickel acetate, is a potent transplacental initiator of epithelial tumors in the fetal rat kidney and a complete transplacental carcinogen for the rat pituitary.

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds

Species, Strain, Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first.)	Reference
NTP (1996) Studies						
Rat, F344/N, both sexes	Normal atmospheric conditions both sexes	Nickel subsulfide	0, 0.15, or 1 mg/m^3 by inhalation	6hr/day, 5 day/wk, 104 wk	The mortality rate of experimental rats was not significantly different from that of control rats. **Male:** Lung: alveolar/bronchiolar adenoma (0/53, 3/53, 6/53*); alveolar/bronchiolar carcinoma (0/53, 3/53, 7/53*); alveolar/bronchiolar adenoma or carcinoma (0/53, 6/53*, 11/53**) Adrenal Medulla: benign pheochromocytoma (13/53, 30/52**, 37/53**); malignant pheochromocytoma (0/53, 2/52, 11/53**); all pheochromocytoma (14/53, 30/52**, 42/53**) **Female:** Lung: alveolar/bronchiolar adenoma (2/53, 5/53, 5/53); alveolar/bronchiolar carcinoma (0/53, 0/53, 4/53); alveolar/bronchiolar adenoma or carcinoma (2/53, 5/53, 9/53*) Adrenal Medulla: benign pheochromocytoma (2/53, 7/53, 36/53**); benign or malignant pheochromocytoma (3/53, 7/53, 36/53**) *$p<0.05$ vs. controls; **$p<0.01$	NTP (1996b)
Mice, B6C3F$_1$, both sexes	Normal atmospheric conditions both sexes	Nickel subsulfide	0, 0.6, or 1.2 mg/m^3 by inhalation	6 h/day, 5 day/wk, 105 wk	The mortality rate of experimental mice was not significantly different from that of control mice. There were no neoplastic effects in experimental groups of 60 male or 60 female mice.	NTP (1996b)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first.)	Reference
Rats, F344/N, both sexes	Normal atmospheric conditions both sexes	Nickel oxide	0, 0.62, 1.25, or 2.5 mg/m^3 by inhalation	6 h/day, 5 day/wk, 104 wk	The mortality rate of experimental rats was not significantly different from that of control rats. **Male:** Lung: alveolar/bronchiolar adenoma (0/54, 1/53, 3/53, 2/52); alveolar/bronchiolar carcinoma (0/54, 0/53, 3/53, 2/52); alveolar/bronchiolar adenoma or carcinoma (0/54, 1/53, 6/53*, 4/52*); Adrenal medulla: benign pheochromocytoma (27/54, 24/52, 26/53, 32/52); malignant pheochromocytoma (0/54, 0/52, 1/53, 6/52*); benign or malignant pheochromocytoma (27/54, 24/52, 27/53, 35/52*) **Female:** Lung: alveolar/bronchiolar adenoma (1/53, 0/53, 1/53, 4/54); alveolar/bronchiolar carcinoma (0/53, 0/53, 5/53*, 1/54); alveolar/bronchiolar adenoma or carcinoma (1/53, 0/53, 6/53, 5/54) Adrenal medulla: benign pheochromocytoma (4/51, 7/52, 6/53, 18/53**) *p<0.05 vs. controls; **p<0.01	NTP (1996a)
Mice, B6C3F$_1$, both sexes	Normal atmospheric conditions both sexes	Nickel oxide	0, 1.25, 2.5, or 5 mg/m^3 by inhalation	6 h/day, 5 day/wk, 104 wk	The mortality rate of experimental mice was not significantly different from that of control mice. **Male**: No neoplastic effects. **Female**: (Uncertain Findings) Lung: alveolar/bronchiolar adenoma (2/64, 4/66, 10/63*, 3/64); alveolar/bronchiolar carcinoma (4/64, 11/66, 4/63, 5/64); alveolar/bronchiolar adenoma or carcinoma (6/64, 15/66*, 12/63, 8/64) *p<0.05 vs. controls	NTP (1996a)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first)	Reference
Rats, F344/N, both sexes	Normal atmospheric conditions both sexes	Nickel sulfate hexahydrate	0, 0.12, 0.25, 0.5 mg/m^3 by inhalation	6 h/day, 5 day/wk, 104 wk	The mortality rate of experimental rats was not significantly different from that of control rats. There were no neoplastic effects in experimental groups of 53-55 male or female rats.	NTP (1996c)
Mice, B6C3F_1, both sexes	Normal atmospheric conditions both sexes	Nickel sulfate hexahydrate	0, 0.25, 0.5, or 1 mg/m^3 by inhalation	6 h/day, 5 day/wk, 104 wk	The mortality rate of experimental mice was not significantly different from that of control mice. There were no neoplastic effects in experimental groups of 60-62 male or female mice.	NTP (1996c)
Nickel subsulfide						
Mice, CH3, male Mice, B6C3F1, male Mice, C57BL, male	Injection vehicle alone	Nickel subsulfide	0, 0.5, 1.0, 2.5, 5.0, or 10.0 mg/site injected into the thigh musculature of both hind limbs	Single dose at age 6 to 8 wk and observed for 78 wk.	The mortality rate of C3H and B6C3F_1 mice injected with 5 mg/site and over was greater than that of control mice as was the mortality rate of C57BL mice at any dose of nickel subsulfide. **C3H:** Injection site sarcomas: 0/30, 5/30, 10/30, 20/27, 28/29, 14/14, respectively **B6C3F1:** Injection site sarcomas: 0/30, 2/29, 8/30, 15/30, 16/20, 5/6, respectively **C57BL:** Injection site sarcomas: 0/24, 1/27, 4/28, 6/21, 6/15, 0/2, respectively	Rodriguez et al. (1996)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Controls	Chemical Form and Dose, Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first.)	Reference
Rats, F344/NCr, male	1) 0.1 mL water 2) 0.5 mg *Mycobacterium Bovis* antigen (MB) 3) 1.0 mg cortisol 4) 1.0 mg indomethacin	**Group 1**: 2.5 mg Ni_3S_2 i.m. injection alone **Group 2**: 2.5 mg Ni_3S_2 + 0.5 mg MB i.m. injection **Group 3**: 2.5 mg Ni_3S_2 + 1.0 mg cortisol i.m. injection **Group 4:** 2.5 mg Ni_3S_2 + 1.0 mg indomethacin i.m. injection **Group 5:** 2.5 mg Ni_3S_2 i.m. injection + 1.0 mg MB sc. injection **Group 6**: 2.5 mg Ni_3S_2 i.m. injection + 2.0 mg indomethacin s.c. injection	Single injection at 8 wk of age and obsderved for up to 71 wk	The mortality rate of experimental rats was not significantly different from that of control rats. **Group 1:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 17/20) **Group 2:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 1/20) **Group 3:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 17/20) **Group 4:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 16/20) **Group 5:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 20/20) **Group 6:** Cumulative number of rats with injection site tumors: (0/20, 0/20, 0/20, 0/20, 19/20)	Kasprzak and Ward (1991)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Controls	Chemical Form	Dose Route	Exposure Duration	Results/Comments (Control group incidence ratios, if reported, listed first.)	Reference
Rats, F344/NCr, male	6.2 mg MgCarb (n = 20), 3.4 mg Fe^0 (n = 20), 0.1 mL water inj. vehicle (n = 20)	5 mg Ni_3S_2 (Group 1, n = 40) 5 mg Ni_3S_2 + 6.2 mg MgCarb (Group 2, n = 20) 5 mg Ni_3S_2 + 3.4 mg Fe^0 (Group 3, n = 20)	2 intrarenal injections	Observation began 24 wk post injection and lasted until week 109	The mortality rate of experimental rats was not significantly different from that of control rats. **Group 1:** Cumulative number of rats with renal tumors: (0/20, 0/20, 0/20, 25/40) **Group 2:** Cumulative number of rats with renal tumors: (0/20, 0/20, 0/20, 4/20) **Group 3:** Cumulative number of rats with renal tumors: (0/20, 0/20, 0/20, 12/20) First 3 incidences in parentheses are control groups	Kasprzak et al. (1994)
Nickel acetate						
Rats, F344/NCr, male (n = 23, 24)	Saline (n = 24)	Nickel acetate tetrahydrate (NiAcet), or NiAcet followed by sodium barbital (NaBB)	NiAcet = 90 µmol/ kg body weight, i.p. NaBB; 500 ppm in drinking water	Single injection at 5 wk of age, or single injection at 5 wk of age + exposure to NaBB through drinking water 2 wk later. Survivors sacrificed at 101 wk of age.	Mortality was significantly greater in rats given NaBB following NiAcet injection than in rats given only NiAcet. **NiAcet only:** Renal cortical lesions: Adenomas (0/24, 1/23), carcinomas (0/24, 0/23) Renal pelvic tumors: Papillomas (0/24, 0/23), carcinomas (0/24, 0/23) **NiAcet + NaBB:** Renal cortical tumors: Adenomas (0/24, 13/24*), carcinomas (0/24, 4/24) *$p<0.0002$ compared to NiAcet-only rats Renal pelvic tumors: Papillomas (0/24, 8/24), carcinomas (0/24, 0/24)	Kasprzak et al. (1990)

Table 4-1. Post-IARC (1990) Experimental Carcinogenicity Studies of Nickel Compounds (Continued)

Species, Strain, Sex	Chemical Form	Dose, Route	Exposure Duration	Results/Comments (Control group incidence listed first)	Reference
Rats, F344/NCr, sex n.p.	Nickel acetate (NiAcet) in distilled water Sodium barbital (NaBB)	**Group 1:** pregnant rats given NiAcet 90 µmol/kg i.p.; offspring divided into groups given tap water as drinking water (**Group 1A**) or 0.05% NaBB in drinking water (**Group 1B**) **Group 2**: pregnant rats given NiAcet 45 µmol/kg i.p.; offspring divided into groups given tap water as drinking water (**Group 2A**) or 0.05% NaBB in drinking water (**Group 2B**) control group given sodium acetate	**Group 1:** pregnant rats treated once/day on day 17 of gestation **Group 2:** pregnant rats treated twice on days 16 and 18 of gestation male and female offspring observed until age 85 wk	Neoplastic lesions in offspring: **Group 1A males**: total renal tumors (0/15, 0/17) total pituitary tumors (1/15, 9/17[a]) **Group 1B males:** total renal tumors (1/15, 8/15*) total pituitary tumors (2/15, 6/15) **Group 1A females:** total renal tumors (0/16, 0/16) total pituitary tumors (3/16, 5/16[a]) **Group 1B females:** total renal tumors (0/14, 0/15) total pituitary tumors (4/14, 5/15) **Group 2A males**: total renal tumors (0/15, 0/15) total pituitary tumors (1/15, 6/15[b]) **Group 2B males:** total renal tumors (1/15, 7/15*) total pituitary tumors (2/15, 7/15) **Group 2A females:** total renal tumors (0/16, 0/16) total pituitary tumors (3/16, 8/16[b]) **Group 2B females:** total renal tumors (0/14, 0/15) total pituitary tumors (4/14, 6/15) *p<0.01 vs. controls [a] p=0.012 vs. controls; both sexes combined b p=0.008 vs. controls; both sexes combined	Diwan et al. (1992)

5.0 GENOTOXICITY

5.1 Review of Animal Genotoxicity Studies (IARC, 1990)

IARC (1990) reviewed data on the genotoxic effects of nickel compounds. The summary of results for studies in mammalian systems is presented as follows: metallic nickel; nickel oxides and hydroxides; crystalline nickel sulfide and subsulfide, amorphous nickel sulfide; nickel chloride, nickel sulfate, nickel acetate, nickel nitrate; and, nickel carbonate, nickel subselenide, nickel potassium cyanide, and nickelocene.

5.1.1 Metallic Nickel

Nickel powder induced a dose-dependent increase in morphological transformations of Syrian hamster embryo cells *in vitro* (Costa et al., 1981).

5.1.2 Nickel Oxides and Hydroxides

The cell-transforming activity of nickel monoxide was correlated with its ability to induce preneoplastic changes in rats (Sunderman et al., 1987). Nickel trioxide transformed Syrian hamster embryo cells at twice the rate of nickel monoxide (Costa et al., 1981).

5.1.3 Crystalline Nickel Sulfide, Crystalline Nickel Subsulfide, and Amorphous Nickel Sulfide

In cultured Chinese hamster ovary cells, DNA repair (Robison et al.,1983), single-strand breaks (Robison and Costa, 1982), a dose-dependent increase in SCE, and a dose- and time-dependent increase in the frequency of chromosomal aberrations (Sen and Costa; 1985,1986) occurred after treatment with crystalline nickel sulfide. Crystalline nickel sulfide induced chromosomal aberrations, including gaps, breaks, and exchanges, in Chinese hamster ovary cells (Nishimura and Umeda, 1979; Umeda and Nishimura, 1979). Crystalline nickel sulfide induced DNA strand breaks in rat primary hepatocytes (Sina et al., 1983). Single-strand breaks and DNA protein cross-links were the two main lesions induced by crystalline nickel sulfide (Costa et al.,1982; Patierno and Costa, 1985).

Particulate crystalline nickel subsulfide induced resistance to 8-azaguanine in cultured rat liver cells, but neither particulate nor dissolved nickel subsulfide induced unscheduled DNA synthesis in primary rat hepatocytes (Swierenga and Mclean, 1985). Crystalline nickel subsulfide induced a dose-dependent increase in the frequency of morphological transformations in primary Syrian hamster embryo cells (DiPaolo and Casto, 1979). Robison et al. (1982, 1983) showed that crystalline nickel subsulfide induced strand breaks in hamster embryo cells, but amorphous nickel sulfide, which is not phagocytized by cells, had no effect on Syrian or Chinese hamster embryo cells. Crystalline nickel subsulfide and amorphous nickel sulfide induced a weak mutation response at the *hprt* locus in Chinese hamster ovary cells (Costa et al., 1980). Amorphous nickel sulfide had no effect on Chinese hamster ovary cells or Syrian hamster embryo cells (Robison et al., 1983).

5.1.4 Nickel Chloride, Nickel Sulfate, Nickel Acetate, and Nickel Nitrate

In Chinese hamster ovary cells, nickel chloride increased the frequency of strand breaks (Robison and Costa, 1982), SCE, and chromosomal aberrations (Sen and Costa, 1985, 1986; Sen

et al., 1987), and induced single-strand breaks, DNA-protein cross-links (Patierno and Costa, 1985), and DNA repair synthesis (Robison et al. 1983, 1984). Nickel chloride also induced chromosomal aberrations (Larramendy et al.,1981) and morphological transformations (Pienta et al., 1977; DiPaolo and Casto, 1979) in Syrian hamster embryo cells. Nickel chloride increased the frequency of chromosomal aberrations in bone-marrow cells of Chinese hamsters (Chorvatovicová, 1983) and Swiss mice (Mohanty, 1987).

In Chinese hamster V79 cells, nickel chloride induced 8-azaguanine-resistant mutations (Miyaki et al., 1979), a dose-related increase in the frequency of mutation to 6-thioguanine resistance (Hartwigg and Beyersmann, 1989), and a dose-dependent depression of proliferation and mitotic rate (Skreb and Fischer, 1984). It did not induce polychromatic erythrocytes or dominant lethal mutations in BALB/c mice (Deknudt and Léonard, 1982). Nickel chloride inhibited DNA synthesis in embryo cells (Basrur and Gilman, 1967) and liver epithelial cells (Swierenga and McLean, 1985) of rats.

Nickel sulfate caused an increased frequency of SCE in Chinese hamster Don cells (Ohno et al., 1982), Chinese hamster ovary cells (Deng and Ou, 1982), and in Syrian hamster embryo cells (Larramendy et al., 1981) Nickel sulfate hexhydrate induced a concentration-dependent increase in morphological transformation of Syrian hamster cells (Pienta et al., 1977; DiPaolo and Casto, 1979; Zhang and Barrett, 1988). Increased frequencies of chromosomal aberrations were seen in Syrian hamster embryo cells exposed to nickel sulfate hexahydrate (Larramendy et al., 1981). The frequency of chromosomal aberrations was not increased in bone-marrow cells and spermatogonia of male albino rats after intraperitoneal injections of nickel sulfate (Mathur et al., 1978).

5.1.5 Nickel Carbonate, Nickelocene, Nickel Potassium Cyanide, and Nickel Subselenide

Nickel carbonate induced DNA damage in rat kidney cells *in vivo* (Ciccarelli et al., 1981). Crystalline nickel subselenide transformed cultured primary Syrian hamster embryo cells (Costa et al., 1981; Costa and Mallenhauer, 1980), and nickel potassium cyanide increased the frequency of chromosomal aberrations in mouse mammary carcinoma cells (Nishimura and Umeda, 1979; Umeda and Nishimura, 1979). Bacterial gene mutations were not induced by nickelocene (Haworth et al., 1983). Nickel (II) and nickel (III) tetraglycine complexes induced DNA damage in calf thymus nucleohistone (Kasprzak and Bare, 1989).

5.2 Review of Human Genotoxicity Studies (IARC, 1990)

5.2.1 Metallic Nickel

Nickel powder did not induce chromosomal aberrations in cultured human peripheral lymphocytes (Paton and Allison, 1972).

5.2.2 Nickel Oxides and Hydroxides

Nickel monoxide did not induce chromosomal aberrations in cultured human peripheral lymphocytes (Paton and Allison, 1972), but did induce anchorage-independent growth in primary human diploid foreskin fibroblasts (Biedermann and Landolph, 1987).

5.2.3 Nickel Sulfides

Crystalline nickel subsulfide and amorphous nickel sulfide increased the frequency of SCE in cultured human lymphocytes (Saxholm et al., 1981), and induced anchorage-independent growth in human skin fibroblasts (Biedermann and Landolph, 1987).

5.2.4 Nickel Sulfate and Nickel Chloride

Dose-dependent increases in the frequency of SCE were seen in human blood peripheral lymphocytes exposed to nickel sulfate (Larramendy et al., 1981). Nickel sulfate did not induce DNA single-strand breaks in human fibroblasts (Fornace, 1982). Nickel sulfate reduced average chromosomal length in human lymphocytes (Andersen, 1985), transformed normal human bronchial epithelial cells (Lechner et al., 1984), and induced transformation to anchorage-dependent growth of primary human foreskin fibroblasts (Biedermann and Landolph, 1987). Human fetal kidney cortex explants did not become tumorigenic after 70-100 days of exposure to nickel sulfate (Tveito et al., 1989). In two human cell lines, exposure to nickel chloride *in vitro* resulted in a dose-dependent depression of proliferation and mitotic rate (Skreb and Fischer, 1984).

5.2.5 Mixed Exposures

A study of two groups of nickel refinery workers employed at the same Norwegian plant showed no increase in the frequency of SCE in mitogen-stimulated peripheral blood lymphocytes of workers exposed to nickel compounds during processing operations, though there was a statistically significant ($p<0.003$) increase in chromosomal aberrations in comparison to controls (Waksvik and Boysen, 1982). In the first group, nine workers who had similar nickel exposures (average air concentration of 0.5 mg Ni/m^3) for an average of 21.2 years showed an increased frequency of gaps (11.9%) compared to a control group of unexposed workers (3.7%). In the second group, 11 workers who had similar nickel exposures (average air concentration of 0.2 mg/m^3) for an average of 25.2 years also showed an increased frequency of gaps (18.3%) as compared to the control group (Waksvik and Boysen, 1982). Breaks in the two groups did not differ significantly from controls and the difference in the percentage of gaps between the nickel-exposed workers was not statistically significant.

In a study of retired nickel workers who had been employed at the same plant as the workers in the studies described above, an increased frequency of gaps (7.6%, $p<0.05$) and breaks (4.1%, $p<0.001$) was detected in comparison to controls (5.3%, 0.5%, respectively). These workers had been exposed to an air nickel concentration higher than 1.0 mg/m^3 for more than 25 years (Waksvik et al., 1984).

An increased frequency of chromosomal gaps, breaks, and fragments (4.3% versus 0.8% in controls) was observed in a study of seven electroplating workers exposed to nickel and chromium compounds (Deng et al., 1983, 1988). These workers were exposed to an air nickel

concentration of 0.0053-0.094 mg/m^3 for 2-27 years. The Working Group noted a small increase in the frequency of SCE in exposed workers.

5.3 Animal Genotoxicity Studies Published Post-IARC (1990)

[Excludes (with the exception of Higinbotham et al., 1992) those studies reviewed by NTP (1996)]

In calf thymus DNA, Ni^{2+} was effective in causing 8-hydroxy-2'-deoxyguanosine (8-OH-dG) formation and double-strand DNA breaks. A mechanism of 8-OH-dG formation was suggested by the involvement of free radicals in this formation, and inhibition by chelating agents (Shi et al., 1995).

In another study of DNA base damage, male F344/NCr rats were injected i.p. with 90 mmoles Ni(II) acetate tetrahydrate/kg body weight. The results indicated a tissue-specific response to Ni(II)-mediated oxidative DNA base damage, with apparently greater lesion persistence in the kidney than in the liver, consistent with the kidney as a primary target of Ni(II) carcinogenicity from soluble salts (Kasprzak et al., 1997). In rat kidney, the frequency of transforming mutations in the K-*ras* oncogene induced by an injection of nickel subsulfide was increased by coadministration of iron (Higinbotham et al., 1992). These findings are consistent with the known ability of nickel, in the presence of an oxidizing agent, to catalyze formation of 8-OH-dG, which leads to misincorporation of dATP opposite the oxidized guanine residue.

DNA damage (single-strand breaks) was not seen in cultured lung, liver, or kidney cells of rats administered 44.4 mg nickel chloride/kg s.c., either alone or in combination with cadmium chloride administered i.p. just prior to treatment with nickel chloride (Saplakoglu et al., 1997).

5.4 Human Genotoxicity Studies Published Post-IARC (1990)

Kiilunen et al. (1997) found that the frequency of micronucleated epithelial cells in the buccal mucosa of nickel refinery workers in the Helsinki area was not significantly elevated versus controls. Furthermore, there was no correlation between micronucleus frequencies and levels of nickel in the air in the refinery, or in the urine or blood of refinery workers.

Gennart et al. (1993), in an investigation of 24 male workers occupationally exposed for at least two years to varying concentrations of iron, nickel, chromium, and cobalt metal powders, found the mean SCE score of the group to be significantly increased versus the control group (23 male clerical workers matched for age, smoking habits, and alcohol consumption). Nine exposed workers had a mean score above the highest score observed in the controls. Since studies on cobalt have shown the metal to be weakly mutagenic, the investigators concluded that solubilized nickel (and chromium) probably induced the increase in SCE.

5.5 Cogenotoxicity

The details of this study (Lynn et al., 1994) are presented in Table 5-2. The genotoxic effects of nickel chloride were investigated in the presence and absence of UV light, methyl methane sulfonate (MMS), and buthionine sulfoxamine (BSO). Results indicate that UV-induced cyto- and genotoxicity is enhanced by the presence of nickel which may be due to its inhibition of DNA repair.

Table 5-1. Genotoxicity of Nickel Studies Published Post-IARC (1990)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
5.1.1 *Acellular Systems*							
Calf thymus DNA	Liberation of 8-hydroxy-2'-deoxyguanosine (8-OH-dG). Detection via HPLC.	-	$NiCl_2$	Incubation of 1 mM Ni^{2+}, 0.75 mM dG (purified from residues in calf thymus DNA), 10 mM *t*-butyl hydroperoxide, and 2 mM glutathione (GSH)	positive	Generation of 8-OH-dG (approx. 0.2% yield). Ni^{2+} is capable of causing 8-OH-dG and DNA double-strand breaks. Lipid peroxide free radicals are involved in the mechanism of 8-OH-dG formation. Chelating agents inhibit 8-OH-dG formation.	Shi et al. (1995)

Table 5-1. Genotoxicity of Nickel Studies Published Post-IARC (1990) (Continued)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
5.1.2 *In Vivo Mammalian Systems*							
Male F344/NCr rats (5 wk old) 48 animals	DNA damage in renal and hepatic chromatin	n.p.	Ni(II) acetate tetrahydrate (purity n.p.)	Treatment group: 90 µmol Ni(II) acetate/kg injected i.p. Control group: 180 µmol sodium acetate/kg injected i.p.	positive	Rats sacrificed at 12 hr and 1, 3, 7, and 14 days post-treatment. Ni(II) acetate-induced oxidative DNA base damage detected in the kidneys and livers. Lesions showed a greater persistence in the kidney than in the liver, consistent with the kidney as a major target of carcinogenesis from soluble nickel salts.	Kasprzak et al. (1997)
Male albino rats (local strain, 8-12 wk old); no. of animals n.p.	DNA damage (single-strand breaks) in rat lung, liver and kidney	n.p.	$CdCl_2$ or $NiCl_2$ (purity n.p.)	Treatment group: $CdCl_2$: 4 mg/kg bw, injected i.p. $NiCl_2$: 44.4 mg/kg bw, injected s.c.	$NiCl_2$: negative	No single-strand breaks were evident in $NiCl_2$-treated tissues, alone or in combination with prior administration of $CdCl_2$.	Saplakoglu et al. (1997)

Table 5-1. Genotoxicity of Nickel Studies Published Post-IARC (1990) (Continued)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
Male Fischer F344/NCr rats (6 wk old) 100 animals	mutational activation of K-*ras* in rat kidney	n.p.	Ni_3S_2; Ni_3S_2/Fe^0; Fe^0 (purity n.p.); 50% aqueous glycerol	all groups injected intrarenally Treatment Group 1: 10 mg of Ni_3S_2 injected intrarenally. Treatment Group 2: Ni_3S_2/Fe^0 [equimolar amounts of nickel and iron (3.4 mg of Fe^0)] Control Group 1: Fe^0 alone Control Group 2: 0.1 mL of 50% aqueous glycerol	positive	The frequency of transforming mutations in the K-*ras* oncogene induced by nickel was increased in the presence of iron. These findings are consistent with the known ability of nickel, in conjunction with an oxidizing agent, to catalyze formation of 8-OH-dG, which leads to misincorporation of dATP opposite the oxidized guanine residue.	Higinbotham et al. (1992)

Abbreviations: i.p. = intraperitoneally; n.p. = not provided; s.c. = subcutaneously

Table 5-2. Cogenotoxicity of Nickel Studies Published Post-IARC (1990)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Dose	Endpoint Response	Comments	Reference
Chinese Hamster Ovary Cells (CHO-K1)	Measurement of cellular GSH levels; colony forming efficiency, frequencies of SCE, and cell cycle progression; repair synthesis of supercoiled plasmid DNA; joining of oligo(dT) molecules by H-bonding to poly (dA) or poly (rA)	n.p.	$NiCl_2$, Ultraviolet (UV) light, methyl methane-sulfonate (MMS), buthionine sulfoxime (BSO)	CHO cells treated with: (1) 0.8 mM MMS (1 hr), then incubated for various times. (2) 0.2 mM MMS alone (20 hr) (3) 4 mM $NiCl_2$ alone (20 hr) (4) UV (24 hr) (5) 0.2 mM MMS (1 hr), followed by 4 mM $NiCl_2$ +500 μM BSO (4 hr) (6) 0.2 mM MMS (1 hr), followed by 4 mM $NiCl_2$ (4 hr) (7) 0.2 mM MMS (1 hr), followed by various doses of $NiCl_2$ (0-4 mM, 4 hr) (8) 6 J/m^2 UV light (irradiation time n.p.), followed by 4 mM $NiCl_2$ (4 hr)	positive	Cellular GSH increased by treatment with MMS or $NiCl_2$, but not UV. Post treatment with $NiCl_2$ synergistically increased GSH levels in MMS-treated cells, but not with UV-treated cells. Pretreatment with *N*-acetylcysteine (GSH precursor) increased clonogenic survival of cells treated with UV + nickel. Nickel inhibited oligonucleotide ligation repair syntheses of UV- or MMS-treated plasmids. GSH relieves nickel inhibition. Results indicate that UV-induced cyto- and geno-toxicity is enhanced by the presence of nickel, which may be due to its inhibition of DNA repair.	Lynn et al. (1994)

Abbreviation: n.p. = not provided

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, and Excretion in Experimental Animals

Various animal models for nickel absorption and biokinetics have been studied. Studies of rats reported that nickel chloride was excreted primarily in the urine, while the oxide was eliminated equally in urine and feces (English, 1981; Carvalho and Zeimer, 1982; cited by IARC, 1990). A biphasic pulmonary clearance (1-2 hours for the first and 120-300 hours for the second) was reported after intratracheal instillation of nickel subsulfide in mice (Valentine and Fisher, 1984; Finch et al., 1987; cited by IARC, 1990).

Half lives of 1-3 days for nickel sulfate, 5 days for nickel subsulfide, and more than 100 days for nickel oxide have been reported for inhaled or intratracheally instilled nickel compounds (Benson et al., 1987; Dunnick et al., 1989; cited by NTP, 1996). Also, in chronic exposure studies with rats and mice, nickel sulfate had the shortest half-life, followed by nickel subsulfide, and nickel oxide. Oral administration resulted in 1-10% absorption of the dose in mice, rats, and dogs. An absorption rate of 1% (in 24 hours) through guinea pig skin was reported (ATSDR, 1992; Neilson et al., 1993; cited by NTP, 1996a, b, and, c).

6.2 Toxicokinetics of Nickel in Humans

The primary routes for nickel exposure are dietary ingestion, dermal absorption, and inhalation. Inhalation is the most serious toxicological exposure concern in the workplace, followed by dermal exposure (NiDI, 1997). Almost 35% of inhaled nickel is absorbed into the blood from the respiratory tract (Bennet, 1984; Grandjean, 1984; Sunderman and Oskarsson, 1991; cited by NTP, 1996). The disposition, absorption, and elimination of nickel particles in the respiratory tract depend largely on particle size and concentration of nickel, minute volume of the individual, mode of breathing (nasal or oronasal), the use of personal protective equipment, personal hygiene, and the work process, among other factors. Additionally, not all particles are inhalable; humans only inhale about half of the particles larger than 30 μm, and this efficiency may be even less for particles of 100-200 μm. Of the inhaled particles, a small percent which are less than 10 μm (most of which are less than 4 μm), settle to the lower regions of the lung. Once inhaled, the particle solubility, concentration, and surface area all play a role in the amount of time required to absorb and excrete associated metals. Smaller, more soluble particles are more rapidly absorbed and excreted because of an increased surface area to volume (NiDI, 1997).

For dermal absorption, penetration through the skin is primarily dictated by the rate at which nickel can pass through the epidermis, with different species of nickel penetrating at markedly different rates. For example, nickel chloride has been shown to penetrate in amounts ranging from 0.23-3.5% of the applied dose, while nickel sulfate may penetrate at levels of up to 50 times lower (NiDI, 1997).

Excretion of systemically absorbed nickel is mainly through the urine. Human volunteers absorbed 25% of an oral dose of nickel sulfate when it was administered in water, as opposed to only 1% administered by food. Half-life values were around 28 hours. Within 4 days, 100% had been recovered in either urine or as unabsorbed nickel in the stool. Nickel may also be eliminated via sweat, the hair, or human breast milk (NiDI, 1997).

6.3 Biokinetics and Evidence of Exposure in Nickel Workers

The ability to predict exposure and related health risks varies depending upon the nickel species evaluated. Nickel compounds lose their original chemical identity upon entering the blood, making it difficult to identify the original source of exposure (Grant and Mushak, 1989). In blood and urine, soluble nickel compounds and nickel metal powder are more easily measured than less soluble nickel compounds (Sunderman et al., 1986). Nickel refinery workers excreted nickel in their urine for up to 6 months after ceasing to work at the plant (Morgan and Rouge, 1983; cited by NTP, 1996). Post-mortem studies of nickel workers show nickel disposition at the highest levels in the lungs, thyroid, and adrenal glands with lesser concentrations in the kidney, liver, heart, spleen, and other tissues (NiDI, 1997).

Nickel has a half-life ranging from 30 to 53 hours in urine for workers exposed to insoluble nickel particles of small diameter (Raithel et al 1982). Some studies have suggested that for workers exposed to insoluble nickel of large particle size, urinary nickel has a longer half-life ranging from months to years (Torjussen and Andersen, 1979; Boysen et al., 1984; Morgan and Rouge, 1984). Reported levels of urinary nickel range from approximately 0.2 to 10 μg Ni/L in non-exposed individuals (Sunderman et al, 1986). In one study (Bernacki et al., 1978), higher urinary concentrations were seen in workers exposed to soluble nickel compounds. The highest value was 813 μg Ni/L reported in a group of electrolytic refinery workers. Mean urinary nickel values ranged from 2.6 μg Ni/L in high nickel alloy production workers to 222 μg Ni/L in electrolytic refinery workers.

The reported half-life of nickel in serum is similar to that in urine. Tossavainen et al. (1980) reported values ranging from 20 to 34 hours in workers exposed to soluble nickel compounds by inhalation. In human volunteers exposed orally to soluble nickel sulfate hexahydrate, a half-life of 11 hours was observed (Christensen and Lagesson, 1981). Nickel concentrations in the serum of nonexposed individuals range from 0.05 to 1.1 μg Ni/L (Sunderman et al., 1986).

7.0 MECHANISMS OF CARCINOGENESIS

The genotoxic effects demonstrated in tests of soluble nickel compounds in a variety of systems suggest that ionic nickel may be the carcinogenic species. In human cells, nickel sulfate increased chromosomal aberrations, and both nickel sulfate and nickel chloride increased the frequencies of SCE. In an assay of calf thymus DNA, nickel chloride induced formation of 8-OH-dG (8-hydroxy-2'-deoxyguanosine) and double-strand DNA breaks (section 5).

Oxidative DNA base damage occurred in the kidneys and liver of male rats treated with Ni(II) acetate. Nickel chloride and nickel nitrate were inactive in assays for induction of dominant lethal mutations and micronuclei. Nickel sulfate did not induce chromosomal aberrations in bone marrow cells, but nickel chloride induced chromosomal aberrations in Chinese hamster and mouse bone marrow cells (section 5).

Animal bioassays indicate that ionic nickel initiates carcinogenesis (section 4). Brief transplacental exposure to soluble nickel was a complete carcinogen in the pituitary gland, inducing malignant neoplasms without additional treatments. Malignant pituitary tumors are rare and their occurrence serves to emphasize the carcinogenic potential of soluble nickel compounds. Renal neoplasms were identified in male rats given nickel acetate by i.p. injection followed by sodium barbital in drinking water. In another study, sodium barbital promoted neoplastic lesions in the offspring of rats exposed to nickel.

Many studies have focused on the mechanism(s) underlying the toxicity of nickel compounds. A 1997 investigation (Oller et al., 1997) concluded that nickel subsulfide is probably carcinogenic to man, but not nickel sulfate hexahydrate. Green nickel oxide may only be toxic at very high doses. The toxicity of these compounds may depend largely on the ability of the compounds to be incorporated into the cell (i.e., solubility); genetic propensity for tumor induction is also a factor.

This idea was recently expanded by Costa (1998) in a model for an epigenetic mechanism of action of non-genotoxic carcinogens. Studies have suggested that water insoluble crystalline nickel compounds were responsible for a high incidence of lung and nasal cancers seen in human and animal studies (IARC, 1990). However, since not all water-insoluble crystalline nickel salts could be shown to induce tumors, it was assumed that factors other than water solubility were involved. Tumor induction was thought to be related to the ability of the compound to enter the cell, or by the ability of the cell to incorporate the compound (i.e., phagocytosis). However, Kasprzak and Ward (1991) found that stimulated phagocytes, rather than enhancing carcinogenic response, actually strongly inhibited muscle tumor development in rats injected with nickel subsulfide.

An investigation with Syrian hamster embryo cells (Costa, 1980) showed that cells undergoing transformation selectively phagocytized the negatively charged crystalline nickel sulfide compounds over positively charged amorphous nickel sulfide particles. However, when a negative charge was induced on the amorphous nickel sulfide particles, they too were phagocytized and were able to exhibit transformation potency equivalent to that of the crystalline nickel sulfide particles (Costa, 1980). Once inside the cell, the compound particles dissolve in the intracellular space, a process which is enhanced by the acidic pH of the cytoplasm surrounding the particles. Thus, transformation appeared to be directly related to the ability of the compound to enter the cell and increase intracellular soluble nickel concentrations (Costa, 1991). However, enhanced phagocytosis actually reduces carcinogenic response of insoluble nickel compounds *in vivo* (Kasprzak and Ward, 1991).

Costa's model is based upon the known ability of carcinogenic nickel compounds to enhance DNA chromatin condensation (Costa, 1991; cited by Costa, 1995; Huang et al., 1994). Although oxygen free radicals may be produced, a high incidence of genetic mutations are not generally noted since most of the damage done by the soluble nickel is to genetically inactivate heterochromatic DNA (Sen et al., 1985; 1986, cited by Costa, 1995). Subsequent methylation of this DNA may suppress genetic activities that are essential for normal cell maintenance. In this model, nickel selectively interacts with heterochromatin and binds to histone H1 and core histone, making them more efficient. Nickel then binds in place of Mg^{2+}, increasing the chromatin

condensation state. This causes neighboring euchromatin to be converted to heterochromatin. The intracellular methylation system recognizes the newly formed, more condensed chromatin. The DNA incorporated into heterochromatin is now methylated, and the DNA methylation pattern is inherited in all daughter cells. DNA found in heterochromatin is hypermethylated to direct protein binding for increased condensation (Costa, 1995).

Because water-soluble nickel salts are not taken up into cells as readily as the particulate compounds previously discussed, they tend to be less toxic in animal models (Costa, 1991; cited by Costa, 1995). However, studies by Kasprzak et al. (1990) also showed that soluble nickel acetate, when administered with the promoter sodium barbital, initiated malignant renal cortical epithelial tumors in Fischer rats. Diwan et al. (1992) showed that soluble nickel acetate was a complete transplacental carcinogen that induced malignant pituitary tumors in rats. Furthermore, in combination with the promoter, the soluble nickel salt was found to be a potent transplacental initiator of epithelial tumors in fetal rat kidney (Diwan et al., 1992). These studies clearly indicate the carcinogenic potential of soluble forms of nickel at sites distant from the site of application and indicate macrophage solubilization is not required for carcinogenesis to occur with nickel.

The other widely proposed mechanism of nickel carcinogenesis is that damage to DNA occurs indirectly through reactive oxygen species (ROS) that are generated in response to the compound. This could occur through phagocytosis of crystalline nickel compounds (Zhong et al., 1990; Lin et al., 1991; both cited by McCoy and Kenney, 1992) allowing ROS-mediated genetic damage to take place (McCoy and Kenney, 1992). However, soluble forms of nickel can also induce lesions *in vivo* or *in vitro* in DNA that are indicative of ROS attack. This proposal is supported by evidence that the antioxidant vitamin E inhibits some chromosomal damage caused by nickel (Lin et al., 1991; cited by McCoy and Kenney, 1992).

Overall, it appears that the ionic form of nickel is the ultimate carcinogenic species, and biokinetic factors may dictate the carcinogenic potential of the various soluble or insoluble nickel compounds.

8.0 References

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APPENDIX A

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risks to Humans
Volume 49 (Chromium, Nickel and Welding)
Nickel and Nickel Compounds
pp. 257-445, 616-638, 1990

NICKEL AND NICKEL COMPOUNDS

Nickel and nickel compounds were considered by previous IARC Working Groups, in 1972, 1975, 1979, 1982 and 1987 (IARC, 1973, 1976, 1979, 1982, 1987). Since that time, new data have become available, and these are included in the present monograph and have been taken into consideration in the evaluation.

1. Chemical and Physical Data

The list of nickel alloys and compounds given in Table 1 is not exhaustive, nor does it necessarily reflect the commercial importance of the various nickel-containing substances, but it is indicative of the range of nickel alloys and compounds available, including some compounds that are important commercially and those that have been tested in biological systems. A number of intermediary compounds occur in refineries which cannot be characterized and are not listed.

1.1 Synonyms, trade names and molecular formulae of nickel and selected nickel-containing compounds

Table 1. Synonyms (Chemical Abstracts Service names are given in bold), trade names and atomic or molecular formulae or compositions of nickel, nickel alloys and selected nickel compounds

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Metallic nickel and nickel alloys				
Nickel	7440-02-0 (8049-31-8; 17375-04-1; 39303-46-3; 53527-81-4; 112084-17-0)	C.I. 77775; N1; Ni 233; Ni 270; Nickel 270; Nickel element; NP 2	Ni	0

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Ferronickel	11133-76-9 (11148-37-1; 12604-55-6)	**Iron alloy (base), Fe,Ni**; nickel alloy (non-base), Fe, Ni	Fe, Ni	0
Nickel aluminium alloys	61431-86-5 37187-84-1	**Raney nickel**; Raney alloy	NiAl	0
Nickel-containing steels[c]	12681-83-3	**Iron alloy (base)**; 21-6-9; 21-6-9 alloy; Alloy 21-6-9; AMS 5656C; Armco 21-6-9; ASTM XM10; 21-6-9 austenitic steel; Nitronic 40; Nitronic 40 stainless steel; Pyromet 538; 21-6-9 Stainless steel; Stainless steel 21-6-9; 21-6-9 steel; Steel 21-6-9	Fe 60-69, Cr 18-21, Mn 8-10, Ni 5-7, Si 0-1, N 0.2-0.4, C 0-0.1, P 0-0.1	0
High nickel alloys[c]	12605-70-8	**ASTM B344-60Ni, 16 Cr**; Chromel C; 06Kh15N60; Kh15N60N; Nichrome; NiCr 60/15; PNKh; Tophet C	Ni 57-62, Fe 22-28, Cr 14-18, Si 0.8-1.6, Mn 0-1, C 0-0.2	0
	11121-96-3	AFNOR ZFeNC45-36; AISI 332; Alloy 800; **ASTM B163-800**; DIN 1.4876; IN 800; Incoloy alloy 800; JIS NCF 800; NCF Steel; NCF 800 HTB; Pyromet 800; Sanicro 31; Thermax 4876; TIG N800	Fe 39-47, Ni 30-35; Cr 19-23, Mn 0-1.5, Si 0-1; Cu 0-0.8; Al 0-0.6; Ti 0-0.6; C 0-0.1	0
	12675-92-2	**Haynes alloy No. 188**	Ni(Co)	0
	11105-19-4	Alloy 400; ASTM B127; **ASTM B164-A**; H3261; Monel alloy 400; Monel (NiCu30Fe)	Ni 63-70; Cu 25-37, Fe 0-2.5, Mn 0-2, Si 0-0.5, C 0-0.3	0
Nickel oxides and hydroxides				
Nickel hydroxide (amorphous	12054-48-7 11113-74-9)	Nickel dihydroxide; nickel (II) hydroxide; nickel (2+) hydroxide; **nickel hydroxide ($Ni(OH)_2$)**; nickelous hydroxide	$Ni(OH)_2$	+2
Nickel monoxide	1313-99-1 11099-02-8	Black nickel oxide[d]; green nickel oxide; mononickel oxide; nickel monooxide; nickelous oxide; **nickel oxide (NiO)**; nickel (II) oxide; nickel (2+) oxide	NiO	+2
	34492-97-2	**Bunsenite (NiO)**		
Nickel trioxide	1314-06-3 (34875-54-2)	Black nickel oxide[d]; dinickel trioxide; nickelic oxide; nickel oxide; nickel (III) oxide; **nickel oxide (Ni_2O_3)**; nickel peroxide; nickel sesquioxide	Ni_2O_3	+3
Nickel sulfides				
Nickel disulfide	12035-51-7	**Nickel sulfide (NiS_2)**	NiS_2	+4
	12035-50-6	**Vaesite (NiS_2)**	NiS_2	+4

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Nickel sulfide (amorphous	16812-54-7 (1344-49-6) 11113-75-0)	Mononickel monosulfide; nickel monosulfide; nickel monosulfide (NiS); nickelous sulfide; nickel (II) sulfide; nickel (2+) sulfide; **nickel sulfide (NiS)**	NiS	+2
	1314-04-1 (61026-96-8)	**Millerite (NiS)**	NiS	+2
Nickel subsulfide	12035-72-2	Nickel sesquisulfide; nickel subsulfide (Ni_3S_2); **nickel sulfide (Ni_3S_2)**; trinickel disulfide	Ni_3S_2	NS
	12035-71-1	**Heazlewoodite (Ni_3S_2)**; Khizlevudite		
Pentlandite	53809-86-2	Pentlandite ($Fe_9Ni_9S_{16}$)	$Fe_9Ni_9S_{16}$	NS
	12174-14-0	Pentlandite	$(Fe_{0.4\text{-}0.6}Ni_{0.4\text{-}0.6})_9S_8$	NS
Nickel salts				
Nickel carbonate	3333-67-3	**Carbonic acid, nickel (2+) salt (1:1)**; nickel carbonate (1:1); nickel (II) carbonate; nickel (2+) carbonate; nickel carbonate ($NiCO_3$); nickel (2+) carbonate ($NiCO_3$); nickel monocarbonate; nickelous carbonate	$NiCO_3$	+2
Basic nickel carbonates	12607-70-4 (63091-15-6)	Carbonic acid, nickel salt, basic; nickel carbonate hydroxide ($Ni_3(CO_3)(OH)_4$); **nickel, (carbonato(2-)) tetrahydroxytri-**	$NiCO_3.2Ni(OH)_2$	+2
	12122-15-5	**Nickel bis(carbonato(2-))hexahydroxypenta-**; nickel hydroxycarbonate	$2NiCO_3.3Ni(OH)_2$	+2
Nickel acetate	373-02-4 (17593-69-0)	**Acetic acid, nickel (2+) salt**; nickel (II) acetate; nickel (2+) acetate; nickel diacetate; nickelous acetate	$Ni(OCOCH_3)_2$	+2
Nickel acetate tetrahydrate	6018-89-9	**Acetic acid, nickel (+2) salt, tetrahydrate**	$Ni(OCOCH_3)_2.4H_2O$	+2
Nickel ammonium sulfates	15699-18-0	Ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$); **sulfuric acid, ammonium nickel (2+) salt (2:2:1)**	$Ni(NH_4)_2(SO_4)_2$	+2
Nickel ammonium sulfate hexahydrate	25749-08-0	Ammonium nickel sulfate ($(NH_4)_2Ni_2(SO_4)_3$); **sulfuric acid, ammonium nickel (2+) salt (3:2:2)**	$Ni_2(NH_4)_2(SO_4)_3$	+2

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
	7785-20-8 (51287-85-5, 55526-16-4)	Ammonium nickel (2+) sulfate hexahydrate; ammonium nickel sulfate ($(NH_4)_2Ni(SO_4)_2$); diammonium nickel disulfate hexahydrate; diammonium nickel (2+) disulfate hexahydrate; diammonium nickel (II) disulfate hexahydrate; nickel ammonium sulfate ($Ni(NH_4)_2(SO_4)_2$) hexahydrate; nickel diammonium disulfate hexahydrate; **sulfuric acid, ammonium nickel (2+) salt (2:2:1), hexahydrate**	$Ni(NH_4)_2(SO_4)_2.6H_2O$	+2
Nickel chromate	14721-18-7	**Chromium nickel oxide ($NiCrO_4$)**; nickel chromate ($NiCrO_4$); nickel chromium oxide ($NiCrO_4$)	$NiCrO_4$	+2
Nickel chloride	7718-54-9 (37211-05-5)	Nickel (II) chloride; nickel (2+) chloride; **nickel chloride ($NiCl_2$)**; nickel dichloride; nickel dichloride ($NiCl_2$); nickelous chloride	$NiCl_2$	+2
Nickel chloride hexahydrate	7791-20-0	**Nickel chloride ($NiCl_2$) hexahydrate**	$NiCl_2.6H_2O$	+2
Nickel nitrate hexahydrate	13478-00-7	Nickel (2+) bis(nitrate)hexahydrate; nickel dinitrate hexahydrate; nickel (II) nitrate hexahydrate; nickel nitrate ($Ni(NO_3)_2$) hexahydrate; nickelous nitrate hexahydrate; **nitric acid, nickel (2+) salt, hexahydrate**	$Ni(NO_3)_2.6H_2O$	+2
Nickel sulfate	7786-81-4	Nickel monosulfate; nickelous sulfate; nickel sulfate (1:1); nickel (II) sulfate; nickel (2+) sulfate; nickel (2+) sulfate (1:1); nickel sulfate ($NiSO_4$); **sulfuric acid, nickel (2+) salt (1:1)**	$NiSO_4$	+2
Nickel sulfate hexahydrate	10101-97-0	**Sulfuric acid, nickel (2+) salt (1:1), hexahydrate**	$NiSO_4.6H_2O$	+2
Nickel sulfate heptahydrate	10101-98-1	**Sulfuric acid, nickel (2+) salt (1:1), heptahydrate**	$NiSO_4.7H_2O$	+2
Other nickel compounds				
Nickel carbonyl	13463-39-3 (13005-31-7, 14875-95-7, 36252-60-5, 42126-46-5, 71327-12-3)	**Nickel carbonyl ($Ni(CO)_4$), (T-4)-**; nickel tetracarbonyl; tetracarbonylnickel; tetracarbonylnickel (0)	$Ni(CO)_4$	0

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Nickel antimonide	12035-52-8 (73482-18-5)	**Antimony compound with nickel (1:1)**; nickel antimonide (NiSb); nickel compound with antimony (1:1); nickel monoantimonide	NiSb	NS
	12125-61-0	**Breithauptite (SbNi)**	NiSb	NS
Nickel arsenides	27016-75-7 (12068-59-6 24440-79-7)	**Nickel arsenide (NiAs)**	NiAs	NS
	1303-13-5 (23292-74-2)	Nickeline; **nickeline (NiAs)**; nicolite	NiAs	NS
	12256-33-6	**Nickel arsenide ($Ni_{11}As_8$)**; nickel arsenide tetragonal	$Ni_{11}As_8$	NS
	12044-65-4	**Maucherite ($Ni_{11}As_8$)**; Placodine; Temiskamite	$Ni_{11}As_8$	NS
	12255-80-0	**Nickel arsenide (Ni_5As_2)**; nickel arsenide hexagonal	Ni_5As_2	NS
Nickel selenide	1314-05-2	Nickel monoselenide; **nickel selenide (NiSe)**	NiSe	NS
	12201-85-3	Maekinenite; **Makinenite (NiSe)**	NiSe	NS
Nickel subselenide	12137-13-2	**Nickel selenide (Ni_3Se_2)**	Ni_3Se_2	NS
Nickel sulfarsenide	12255-10-6	**Nickel arsenide sulfide (NiAsS)**	NiAsS	NS
	12255-11-7	**Gersdorffite (NiAsS)**	NiAsS	NS
Nickel telluride	12142-88-0	Nickel monotelluride; **nickel telluride (NiTe)**	NiTe	NS
	24270-51-7	**Imgreite (NiTe)**	NiTe	NS
Nickel titanate	12035-39-1	Nickel titanate(IV); nickel titanate ($NiTiO_3$); **nickel titanium oxide ($NiTiO_3$)**; nickel titanium trioxide	$NiTiO_3$	+2
Chrome iron nickel black spinel	71631-15-7	CI 77504; **CI Pigment Black 30**; DCMA-13-50-9; nickel iron chromite black spinel	$(Ni,Fe)(CrFe)_2O_4$	NS

Table 1 (contd)

Chemical name	Chem. Abstr. Serv. Reg. Number[a]	Synonyms and trade names	Formula	Oxidation state[b]
Nickel ferrite brown spinel	68187-10-0	**CI Pigment Brown 34**; DCMA-13-35-7	$NiFe_2O_4$	NS
Nickelocene	1271-28-9 (51269-44-4)	Bis(η5-2,4-cyclopentadien-1-yl)nickel; di-π-cyclopentadienylnickel; dicyclopentadienylnickel; nickel, bis(η5-2,4-cyclopentadien-1-yl)-; nickel, di-π-cyclopentadienyl-	π-$(C_5H_5)_2Ni$	+2

[a]Replaced CAS Registry numbers are given in parentheses.

[b]NS, not specified; mixed formal oxidation states of nickel and/or complex coordination in the solid form

[c]Chemical Abstracts Service Registry lists hundreds of these compounds; some typical examples are given.

[d]In commercial usage, 'black nickel oxide' usually refers to the low-temperature crystalline form of nickel monoxide, but nickel trioxide (Ni_2O_3), an unstable oxide of nickel, may also be called 'black nickel oxide'.

1.2 Chemical and physical properties of the pure substance

Known physical properties of some of the nickel compounds considered in this monograph are given in Table 2. Data on solubility refer to saturated solutions of the compound in water or other specified solvents. Nickel compounds are sometimes classed as soluble or insoluble in water; such a classification can be useful in technical applications of the various compounds but may not be relevant to determining their biological activity. Water-soluble nickel compounds include nickel chloride (642 g/l at 20°C) and nickel sulfate (293 g/l at 20°C), while nickel monosulfide (3.6 mg/l at 18°C) and nickel carbonate (93 mg/l at 25°C) are classed as insoluble (Weast, 1986). Compounds with solubilities towards the middle of this range are not easily classified in this way. Different forms of nominally the same nickel compound can have very different solubilities in a given solvent, and particle size, hydration and crystallinity can markedly affect the rate of dissolution. For example, anhydrous nickel sulfate and the hexahydrate are similarly soluble in unbuffered water (Grandjean, 1986), but the hexahydrate dissolves several orders of magnitude faster than the anhydrate.

Table 2. Physical properties of nickel and nickel compounds[a]

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Metallic nickel and nickel alloys					
Nickel	58.69	1455	2730	Lustrous white, hard ferromagnetic metal[b] or grey powder	Soluble in dilute nitric acid; slightly soluble in hydrochloric and sulfuric acids; insoluble in cold or hot water
Ferronickel alloy	–	–	–	Grey solid[c]	Combined properties of metallic iron and nickel, ammonia and alkali hydroxides
Nickel oxides and hydroxides					
Nickel hydroxide	92.70	230	–	Green crystals or amorphous solid	Nearly insoluble (0.13 g/l)[d] in cold water; soluble in acid, ammonium hydroxide
Nickel monoxide	74.69	1984	–	Grey, black or green[c] powder	Insoluble in water (0.0011 g/l at 20°C); soluble in acid, ammonium hydroxide[d]
Nickel sulfides					
Nickel disulfide	122.81	Decomposes at 400[d]	–	Black crystals[c] or powder	Insoluble in water[d]
Nickel sulfide					
Amorphous	90.75	797	–	Black crystals or powder	Nearly insoluble (0.0036 g/l, β-form)[d] in water at 18°C; soluble in aqua regia, nitric acid, potassium hydrosulfide; slightly soluble in acids
α-form	90.75	–	–	–	
β-form	90.75	–	–	Dark-green crystals[c]	
Nickel subsulfide (α-form)	240.19	790	–	Lustrous pale-yellowish or bronze metallic crystals	Insoluble in cold water; soluble in nitric acid

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Nickel salts					
Nickel acetate	176.78	Decomposes	16.6	Dull-green crystals	Soluble in water (166 g/l at 20°C)[d]; insoluble in ethanol
Nickel acetate tetrahydrate	248.84	Decomposes	16	Dull-green crystals	Soluble in water (160 g/l at 20°C)[d]; soluble in dilute ethanol
Nickel ammonium sulfates					
Hexahydrate	394.94	–	–	–	Soluble in water (104 g/l at 20°C)[d]
Anhydrous	286.88	Decomposes[e]	–	Green crystals[e]	Soluble in water (300 g/l at 20°C)[d]; less soluble in ammonium sulfate solution; insoluble in ethanol[e]
Nickel carbonate	118.70	Decomposes	–	Light-green crystals	Nearly insoluble (0.093 g/l) in water at 25°C; insoluble in hot water, soluble in acids
Nickel hydroxycarbonate	587.67	Decomposes	–	Light-green crystals or brown powder[e] or wet green paste	Insoluble in cold water; decomposes in hot water; soluble in acids
Nickel chlorides					
Anhydrous	129.60	1001	Sublimes at 973	Yellow deliquescent scales	Soluble in water at 20°C (642 g/l) and at 100°C (876 g/l); soluble in ethanol, ammonium hydroxide; insoluble in nitric acid
Hexahydrate	237.70	–	–	Green deliquescent crystals	Soluble in water (2540 g/l at 20°C)[d]; very soluble in ethanol
Nickel chromate	174.71	–	–	Black crystals	Insoluble in water

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Nickel nitrate hexahydrate	290.79	56.7	Decomposes at 136.7	Green deliquescent crystals	Soluble in water (2385 g/l at 0°C), ammonium hydroxide and ethanol
Nickel sulfates					
Anhydrous	154.75	Decomposes at 848	–	Pale-green to yellow crystals	Soluble in water (293 g/l at 20°C); insoluble in ethanol and diethyl ether[d,e]
Hexahydrate	262.84	53.3	–	Blue or emerald-green crystals[e]	Soluble in water (625 g/l at 0°C); soluble in ethanol[d]
Heptahydrate	280.85	99	–	Green crystals	Soluble in water (756 g/l at 20°C); soluble in ethanol[d]
Other nickel compounds					
Nickel antimonide	180.44	1158	Decomposes at 1400	Light-copper to mauve crystals[c]	Insoluble in water[d]
Nickel arsenides	133.61	968	–	Grey crystals[c]	Insoluble in hot or cold water, soluble in aqua regia
NiAs					
$Ni_{11}As_8$	1244.96	1000	–	Platinum-grey crystals	Insoluble in water[d]
Ni_5As_2	443.39	993	–	Grey crystals[c]	Insoluble in water[d]
Nickel carbonyl	170.73	–25	43	Colourless to yellow liquid	Nearly insoluble (0.18 g/l) in water at 9.8°C; soluble in aqua regia, ethanol, diethyl ether, benzene, nitric acid; insoluble in dilute acids or dilute alkali

Table 2 (contd)

Chemical name	Atomic/ molecular weight	Melting-point (°C)	Boiling-point (°C)	Typical physical description	Solubility
Nickelocene	188.88	171–173[e]	–	Dark-green crystals[e]	Soluble in most organic solvents; insoluble in water; decomposes in acetone, ethanol, diethyl ether
Nickel selenide (NiSe)	137.65	Red heat	–	White or grey crystals	Insoluble in water and hydrochloric acid; soluble in aqua regia, nitric acid
Nickel subselenide (Ni_3Se_2)	333.99	–	–	Green crystals[c]	Insoluble in water[d]
Nickel telluride	186.29	Decomposes at 600–900[d]	–	Grey crystals[c]	Insoluble in water; soluble in nitric acid, aqua regia, bromine water[d]
Nickel titanate	154.57	Decomposes at 1000	–	Yellow crystals[c]	Insoluble in water[d]

[a]From Weast (1986), unless otherwise specified; –, depending on composition

[b]From Windholz (1983)

[c]From Sunderman (1984)

[d]From Grandjean (1986)

[e]From Sax & Lewis (1987)

1.3 Technical products and impurities

This section does not include nickel-containing intermediates and by-products specific to nickel production and use, which are considered in section 2.

(a) *Metallic nickel and nickel alloys*

Ferronickel contains 20-50% nickel (Sibley, 1985). Other components include carbon (1.5-1.8%), sulfur (<0.3%), cobalt (<2%), silicon (1.8-4%), chromium (1.2-1.8%) and iron (balance of alloy). It is delivered as ingots or granules (ERAMET-SLN, 1986).

Pure unwrought *nickel* is available commercially in the form of cathodes, powder, briquets, pellets, rondelles, ingots and shot. Its chemical composition is >99% nickel, with carbon, copper, iron, sulfur and oxygen as impurities (Sibley, 1985). Metallic nickel undergoes surface oxidation in air; oxidation of finely divided nickel powder can result in the conversion of a large fraction of the metal to oxide upon prolonged storage (Cotton & Wilkinson, 1988).

Nickel-aluminium alloy (for the production of Raney nickel) is available as European Pharmacopoeia grade with the following typical analysis: nickel, 48-52%; aluminium, 48-52%; and chloride, 0.001% (Riedel-de Haën, 1986).

Nickel alloys can be categorized as nickel-chromium, nickel-chromium-cobalt, iron-nickel-chromium and copper-nickel alloys. Typical analyses are given in Table 3. Austenitic steels are the major group of *nickel-containing steels*. Typical compositions are given in Table 4.

(b) *Nickel oxides and hydroxides*

The temperature of formation of *nickel oxide* (up to 1045°C) determines the colour of the crystal (jet-black to apple green), the crystalline surface area and the nickel [III] content (<0.03-0.81% by weight). The temperature of formation may also affect the crystalline structure and the incidence of defects within it (Sunderman *et al.*, 1987; Benson *et al.*, 1988a).

Nickel monoxides are available commercially in different forms as laboratory reagents and as industrial products. Laboratory reagents are either green powder (Aldrich Chemical Co., Inc., 1988) or black powders; industrial products are either black powders, coarse particles (Sinter 75) or grey sintered rondelles (INCO, 1988; Queensland Nickel Sales Pty Ltd, 1989). Sinter 75 (76% Ni) contains about 22% oxygen and small amounts of copper (0.75%), iron (0.3%), sulfur (0.006%) and cobalt (1.0%) (Sibley, 1985). Sintered rondels (≥85% Ni) are formed by partially reducing a cylindrical pressing of granular nickel oxide to nickel metal. The degree of reduction achieved determines the nickel content of the finished rondel (Queensland Nickel Sales Pty Ltd, 1989).

Table 3. Elemental analyses of representative nickel alloys (weight %)[a]

Alloy	Ni	Cu	Cr	Co	Fe	Mo	W	Ta	Nb	Al	Ti	Mn	Si	C	Zr
Nickel–chromium															
Cast alloy 625	63.0	–	21.6	–	2.0	8.7	–	–	3.9	0.2	0.2	0.06	0.20	0.20	–
Hastelloy alloy X	47.0	–	22.0	1.5	18.5	9.0	0.6	–	–	–	–	0.50	0.50	0.10	–
Inconel alloy 617	54.0	–	22.0	12.5	–	9.0	–	–	–	1.0	–	–	–	0.07	–
Nickel–chromium–cobalt															
Haynes Alloy 1002	16.0	–	22.0	Bal	1.5	–	7.0	3.8	–	0.3	0.2	0.70	0.40	0.60	0.30
Haynes Alloy No. 188	22.0	–	22.0	39.0	3.0 max	–	14.0	–	–	–	–	1.25 max	0.40	0.10	–
Nickel–iron–chromium															
Haynes Alloy 556	20.0	–	22.0	20.0	29.0	3.0	2.5	0.9	0.1	0.3	–	1.50	0.40	0.10	–
Incoloy Alloy 800[b]	32.5	–	21.0	–	46.0	–	–	–	–	0.4	0.4	0.80	0.50	0.05	–
Nickel–copper															
Monel alloy 400[b]	66.5	31.5	–	–	1.3	–	–	–	–	–	–	1.0	0.25	0.15	–
Monel alloy K-500[b]	65.0	29.5	–	–	1.0	–	–	–	–	2.8	0.5	0.6	0.15	0.15	–

[a]From Nickel Development Institute (1987a); Bal, balance

[b]From Tien & Howson (1981)

Table 4. Typical composition of nickel-containing steels (weight %)[a]

Grade	Cr	Ni	Mn	Mo	C	Si	S	P	Fe
AISI-201	16-18	3.5-5.5	5.5-7.5	-	0.15	1.0	0.03	0.06	Balance
AISI-302	17-19	8.0-10.0	2.0	-	0.15	1.0	0.03	0.045	Balance
AISI-304	18-20	8.0-10.5	2.0	-	0.08	1.0	0.03	0.045	Balance
AISI-316	16-18	10-14	2.0	2-3	0.08	1.0	0.03	0.045	Balance

[a]From Nickel Development Institute (1987b); AISI, American Iron and Steel Institute

Nickel hydroxide is commercially available at 97% purity (Aldrich Chemical Co., Inc., 1988).

(*c*) *Nickel sulfides*

Nickel sulfide exists in three forms: the high-temperature, hexagonal crystal form, in which each nickel atom is octahedrally coordinated to six sulfur atoms; the low-temperature, rhombohedral form (which occurs naturally as millerite), in which each nickel atom is coordinated to two other nickel atoms and five sulfur atoms (Grice & Ferguson, 1974); and amorphous nickel sulfide. Amorphous nickel sulfide is gradually converted to nickel hydroxy sulfide on contact with air (Cotton & Wilkinson, 1988). Grice and Ferguson (1974) referred to the rhombohedral (millerite) form as β-nickel sulfide and the high-temperature hexagonal form as α-nickel sulfide. Different nomenclatures have been used by other authors (Abbracchio *et al.*, 1981; Grandjean, 1986). The term β-nickel sulfide is used to denote the rhombohedral millerite form throughout this monograph.

Nickel subsulfide exists in two forms: α-nickel subsulfide, the low-temperature, rhombohedral form (heazlewoodite), in which nickel atoms exist in distorted tetrahedral coordination and the sulfur atoms form an almost cubic body-centred sublattice, with six equidistant nickel neighbours; and β-nickel subsulfide, the high-temperature form (Sunderman & Maenza, 1976).

An examination of the surface of crystalline and amorphous nickel sulfide particles revealed that crystalline particles have a net negative surface charge, while the surface charge of amorphous nickel sulfide appears to be positive. X-Ray photoelectron spectroscopy analysis of amorphous and crystalline nickel sulfide showed that the outermost surface of the two compounds differed with respect to the Ni/S ratio and the sulfur oxidation state (Abbracchio *et al.*, 1981).

Nickel sulfides are intermediates in nickel smelting and refining which can be isolated as crude mattes for further processing but are not significant materials of commerce. Most nickel subsulfide is produced as an intermediate in many nickel refining processes (Boldt & Queneau, 1967).

(*d*) *Nickel salts*

Nickel acetate is available as the tetrahydrate at a purity of >97% (Mallinckrodt, Inc., 1987).

Nickel ammonium sulfate hexahydrate is available as analytical reagent-grade crystals at a purity of 99.0% min or at a grade for nickel plating (purity, 99-100%; Riedel-de-Haën, 1986).

Nickel carbonate is available mainly as hydroxycarbonates, such as basic nickel carbonate. Laboratory reagent grades may contain 47.5% or 45% nickel; industrial grades, as green powders or wet pastes, contain approximately 45% nickel (INCO, 1981-82; Pharmacie Centrale, 1988).

Nickel chloride is available as the hexahydrate as a laboratory reagent of >99% purity and as industrial products with about 24.7% nickel. It is also available in industrial quantities as an aqueous solution (ERAMET-SLN, 1985).

Nickel nitrate is available as the hexahydrate at >99% purity and as crystals and flakes (J.T. Baker, 1988).

Nickel sulfate is available as the heptahydrate at >99% purity and as the hexahydrate at 99% purity (Aldrich Chemical Co., Inc., 1988).

(*e*) *Other nickel compounds*

Nickelocene is available in solid form at >90% purity or as an 8-10% solution in toluene (American Tokyo Kasei, 1988).

2. Production, Use, Occurrence and Analysis

2.1 Production

Nickel was first isolated in 1751 by a Swedish chemist, Cronstedt, from an arsenosulfide ore (Considine, 1974).

(*a*) *Metallic nickel and nickel alloys*

Table 5 gives world mine production of nickel by region. Table 6 shows world nickel plant production, including refined nickel, ferronickel and nickel recycled from scrap (Chamberlain, 1988).

Various combinations of pyrometallurgical, hydrometallurgical and vapometallurgical operations are used in the nickel producing industry (Boldt & Queneau, 1967; Evans *et al.*, 1979; Tien & Howsen, 1981; Tyroler & Landolt, 1988). The description that follows is a generalized discussion of some of the more common smelting and refining processes.

Table 5. World mine production of nickel, by region (thousand tonnes)[a]

Region	1982	1983	1984	1985	1986
Albania	6.0	7.2	9.2	9.6	9.7
Australia	87.7	76.6	77.1	85.8	69.9
Botswana	17.8	18.2	18.6	19.6	20.0
Brazil	14.5	15.6	23.6	20.3	23.1
Burma	0.02	0.02	0.02	0.02	0.02
Canada	88.7	128.1	174.2	170.0	181.0
China	12.0	13.0	14.0	25.1	25.5
Colombia	1.8	17.5	21.9	15.5	22.1
Cuba	36.2	37.7	31.8	32.4	32.7
Dominican Republic	5.4	19.6	24.0	25.4	22.1
Finland	6.3	5.3	6.9	7.9	6.5
France (New Caledonia)	60.2	46.2	58.3	73.0	65.1
German Democratic Republic	2.5	2.2	2.0	1.6	1.5
Greece	5.0	16.8	16.7	18.7	17.5
Indonesia	46.0	49.4	47.6	40.6	43.9
Morocco	0.13	–	–	–	–
Norway	0.39	0.36	0.33	0.44	0.40
Philippines	19.7	13.9	13.6	28.2	13.6
Poland	2.1	2.1	2.1	2.0	2.0
South Africa	22.0	20.5	25.1	25.1	25.1
USA	2.9	–	13.2	5.6	1.1
USSR	165.1	170.0	174.2	180.0	186.0
Yugoslavia	4.0	3.0	4.0	5.0	5.0
Zimbabwe	15.8	12.0	12.2	11.1	11.0
Total	622.24	675.28	770.65	802.96	784.82

[a]From Chamberlain (1988)

Table 6. World production of processed nickel by region (thousands of tonnes)[a]

Region	1982	1983	1984	1985	1986
Australia	45.9	41.8	38.7	40.9	41.9
Brazil	3.5	8.3	9.2	13.3	13.5
Canada	58.6	87.2	104.0	100.0	115.0
China	12.0	13.0	14.0	22.5	22.5
Colombia	1.3	13.1	17.1	11.8	18.6
Cuba	9.0	9.3	8.5	8.5	7.7
Czechoslovakia	1.5	3.0	4.5	4.5	4.5
Dominican Republic	5.3	21.2	24.2	25.8	22.0

Table 6 (contd)

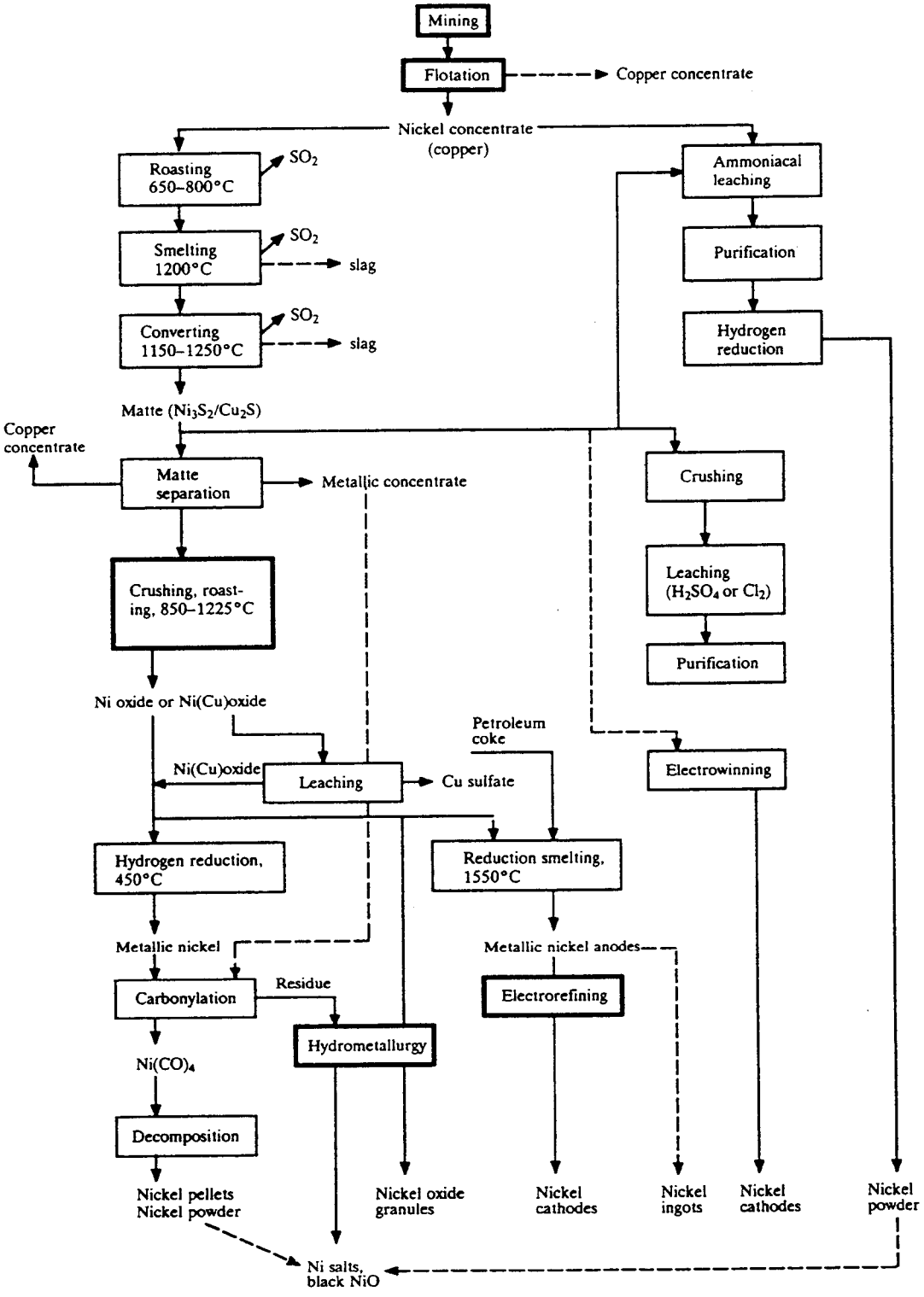
Region	1982	1983	1984	1985	1986
Finland	12.6	14.8	15.3	15.7	16.0
France	7.4	4.9	5.2	7.1	10.0
France (New Caledonia)	28.0	21.7	29.2	36.1	33.0
German Democratic Republic	3.0	3.0	3.0	3.0	3.0
Germany, Federal Republic of	1.2	1.2	1.0	0.7	-
Greece	4.5	12.9	15.8	16.0	12.0
Indonesia	5.0	4.9	4.8	4.8	5.0
Japan	90.6	82.2	89.3	92.7	88.8
Norway	25.8	28.6	35.6	37.5	38.2
Philippines	11.2	6.1	3.5	17.0	2.1
Poland	2.1	2.1	2.1	2.1	2.1
South Africa	14.4	17.0	20.5	20.0	20.0
UK	7.4	23.2	23.3	17.8	31.0
USA	40.8	30.3	40.8	33.0	1.5
USSR	180.0	185.1	191.4	198.0	215.0
Yugoslavia	1.5	1.5	2.0	3.0	3.0
Zimbabwe	13.3	10.2	10.3	9.4	9.8
Total	585.9	646.6	713.3	741.2	736.2

[a]From Chamberlain (1988)

Nickel is produced from two kinds of ore: sulfide and silicate-oxide. The latter occurs in tropical regions, such as New Caledonia, and in regions that used to be tropical, such as Oregon (USA). Both types of ore generally contain no more than 3% nickel (Warner, 1984). Mining is practised by open pit and underground methods for sulfide ores and by open pit for silicate-oxide ores. Sulfide ores are extracted by flotation and magnetic separation into concentrates containing nickel and various amounts of copper and other metals, such as cobalt, precious metals and iron. Silicate-oxide ores are extracted by chemical means.

The extractive metallurgy of sulfide nickel ores (see Fig. 1) is practised in a large variety of processes. Most of these processes begin with oxidation of iron and sulfur at high temperatures in multiple hearth roasters or in fluid bed roasters, or, in the early days, in linear calciners or on travelling grate sinter machines ('sintering'). The roaster calcine is smelted in reverberatory or electric furnaces to remove rock and oxidized iron as a slag, leaving a ferrous nickel (copper) matte. In modern processes, both operations — roasting and smelting — are combined in a single operation called 'flash smelting'. The furnace matte is upgraded by oxidizing and slagging most of the remaining iron in converters. If the converter matte or 'Bessemer matte' contains copper, the matte can be separated into nickel subsulfide, copper sulfide

Fig. 1. Extraction and refining of nickel and its compounds from sulfides ores[a]



[a]Modified from Mastromatteo (1986)

and metallic concentrates by a slow cooling process followed by magnetic concentration and froth flotation.

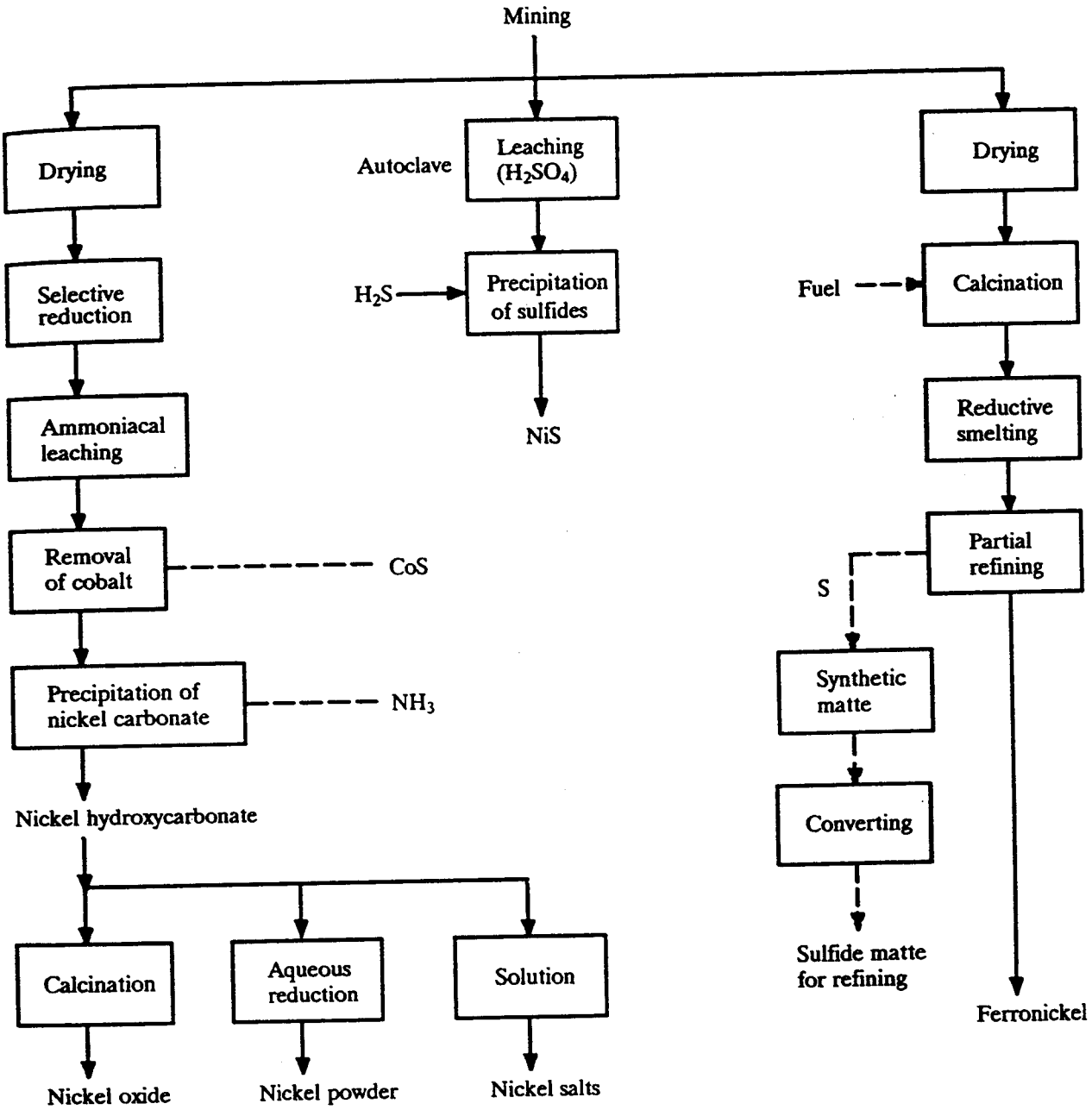
The high-grade nickel subsulfide concentrate is then refined by various processes. Most of them begin with roasting of the concentrate to a crude nickel oxide. When the copper content is low, this crude oxide is directly saleable ('Sinter 75'). In older processes, copper was leached directly from the crude oxide with sulfuric acid (as in Clydach, Wales) or by an acidic anolyte from copper electrowinning (as in Kristiansand, Norway). Refining can be pursued after reducing the crude nickel oxide to metal either in a rotary kiln or in an electric furnace with addition of a carbonaceous reductant. In the first case, the crude particulate metallic nickel is refined by the atmospheric pressure nickel-carbonyl process (Mond carbonyl process) which allows a clear-cut separation of nickel from other metals. Nickel is then produced either as nickel powder or as nickel pellets. The carbonylation residue is further processed to recover precious metals and some nickel and cobalt salts. In the second case, the molten crude nickel is cast into anodes which are 'electrorefined'. The anolyte is purified outside the electrolytic cell by removal of the main impurities, which are iron, arsenic, copper and cobalt. These impurities are generally extracted as filter cakes containing significant amounts of nickel, warranting recycling upstream in the process. Nickel is then produced in the form of electrolytic cathodes or small 'rounds'. This electrorefining process, which was used in Kristiansand, Norway, and Port Colborne, Ontario, is no longer practised there.

The Bessemer nickel (copper) matte can also be refined without roasting, either by a combination of hydrometallurgy and electrolysis ('electrowinning') or by hydrometallurgy alone. There are three types of nickel 'electrowinning' processes: (i) directly from matte cast into (soluble) anodes; (ii) from nickel sulfate solutions obtained by leaching matte with a very low sulfur content; and (iii) from nickel chloride solutions obtained by leaching matte with chloride solution in the presence of chlorine gas. In the three cases, the solutions obtained by dissolving the matte must be purified before plating pure nickel, as for the electrorefining process. In the chloride-electrowinning process, purification is accomplished through solvent extraction methods using tributylphosphate and aliphatic amines diluted in petroleum extracts.

Complete hydrometallurgy can be practised directly on sulfide concentrates or on Bessemer matte by ammonia leaching in sulfate medium in autoclaves. The solution is purified by precipitation of sulfides, and nickel is recovered as metal powder by hydrogen precipitation in autoclaves. The nickel powder can be further sintered into briquettes.

Silicate-oxide ores ('garnierites'/'laterites') are processed either by pyrometallurgy or by hydrometallurgy (Fig. 2). Pyrometallurgy consists of drying, calcining in rotary kilns, then reduction/smelting in electric furnaces. The crude ferronickel

Fig. 2. Extraction and refining of nickel and its compounds from silicate-oxide (laterite) ores[a]



[a]Modified from Mastromatteo (1986)

obtained (containing 20-40% Ni) is partially refined by thermic processes (in ladles) before being cast into ingots or granulated in water. With pyrometallurgy, nickel matte can be produced from silicate-oxide ore either by smelting the ore in the presence of calcium sulfate in a blast furnace (old process) or in an electric furnace, or by direct injection of molten sulfur into molten ferronickel.

Hydrometallurgy of silicate-oxide ores, preferentially poor in silica and magnesia, is practised by ammoniacal leaching or by sulfuric acid leaching. Ammoniacal leaching is used for ore that is selectively reduced in rotary kilns by a mixture of hydrogen and carbon monoxide. Cobalt, the main dissolved impurity, is removed from solution by precipitation as cobalt monosulfide (containing nickel monosulfide). This by-product is further refined to separate and refine nickel and cobalt. The purified nickel stream is then transformed into the hydroxycarbonate by ammonia distillation. The hydroxycarbonate is then dried, calcined and partially reduced to a saleable nickel oxide sinter. Sulfuric acid leaching is conducted under pressure in autoclaves. Nickel and cobalt are extracted from the process liquor by precipitation with hydrogen sulfide, and the mixed nickel-cobalt (10:1) sulfide is further refined in one of the processes described above.

Nickel is obtained not only by recovery from nickel ores but also by recycling process or consumer scrap. Nickel scrap is generated in forming and shaping operations in fabricating plants where nickel-containing materials are used and is also recovered from obsolete consumer goods containing nickel. Small amounts of nickel are also produced as a coproduct of copper and platinum metal refining (Sibley, 1985).

Nickel-containing steels (stainless steels and others) are produced by melting cast iron and adding ferronickel and/or pure nickel or steel scraps in large electric furnaces. The melt is transferred to a refining vessel to adjust the carbon content and impurity levels and is then cast into ingots or continuously into casting shapes. Defects in cast steel are repaired by cutting or scarfing or by chipping or grinding. The desired shapes are produced by a variety of operations, including grinding, polishing and pickling (Warner, 1984). Production volumes of stainless-steel are given in Table 7.

The technology for the production of *nickel alloys* is very similar to that used for steel production, except that melting and decarburizing units are generally smaller, and greater use is made of vacuum melting and remelting (Warner, 1984). In western Europe, it was estimated that 15% of nickel consumption was in nonferrous nickel alloys (Eurométaux, 1986).

Table 7. Stainless-steel[a] production (in thousands of tonnes) in selected regions[b]

Region	1987	1988
Austria	54	67
Belgium	182	254
Finland	189	206
France	720	784
Germany, Federal Republic of	957	1186
Italy	550	623
Spain	327	426
Sweden	457	482
United Kingdom	393	427
Yugoslavia	30	30
Total Europe	3859	4485
USA	1840	1995
Japan	2722	3161
Other countries	787	798
Total	9208	10 439

[a]Stainless steels with and without nickel
[b]ERAMET-SLN (1989a)

(*b*) *Nickel oxides and hydroxides*

Nickel oxide sinter (a coarse, somewhat impure form of nickel monoxide) is manufactured by roasting a semipure nickel subsulfide at or above 1000°C or by decomposing nickel hydroxycarbonate. The sinters produced commercially contain either 76% nickel or, in partially reduced form, 90% nickel. Nickel oxide sinter is produced in Australia, Canada and Cuba (Sibley, 1985).

Green nickel oxide, a finely divided, relatively pure form of nickel monoxide, is produced by firing a mixture of nickel powder and water in air at 1000°C (Antonsen, 1981). Nickel monoxide is currently produced by two companies in the USA, six in Japan, two in the UK and one in the Federal Republic of Germany (Chemical Information Services Ltd, 1988).

Black nickel oxide, a finely divided, pure nickel monoxide, is produced by calcination of nickel hydroxycarbonate or nickel nitrate at 600°C (Antonsen, 1981). It is produced by one company each in Argentina, Brazil, Canada, Japan, Mexico, the UK and the USA (Chemical Information Services Ltd, 1988).

Nickel hydroxide is prepared by (1) treating a nickel sulfate solution with sodium hydroxide to yield a gelatinous nickel hydroxide which forms a fine precipitate when neutralized, (2) electrodeposition at an inert cathode using metallic nickel as the anode and nickel nitrate as the electrolyte, or (3) extraction with hot alcohol of the gelatinous precipitate formed by nickel nitrate solution and potassium hydroxide (Antonsen, 1981). Nickel hydroxide is currently produced by four companies in Japan, three in the USA and one each in the Federal Republic of Germany and the UK (Chemical Information Services Ltd, 1988).

(*c*) *Nickel sulfides*

Purified *nickel sulfide* can be prepared by (i) fusion of nickel powder with molten sulfur or (ii) precipitation using hydrogen sulfide treatment of a buffered solution of a nickel[II] salt (Antonsen, 1981).

Nickel subsulfide can be made by the direct fusion of nickel with sulfur. Impure nickel subsulfide is produced during the processing of furnace matte.

Nickel sulfide and nickel subsulfide are formed in large quantities as intermediates in the processing of sulfidic and silicate-oxide ores and are traded and transported in bulk quantities for further processing. No data on production volumes are available for any of the nickel sulfides.

(*d*) *Nickel salts*

Nickel acetate is produced by heating nickel hydroxide with acetic acid in the presence of metallic nickel (Sax & Lewis, 1987). This salt is currently produced by six companies in the USA, three each in Argentina, Brazil, Italy, Japan and the UK, two each in the Federal Republic of Germany and Mexico, and one each in Australia and Spain (Chemical Information Services Ltd, 1988).

An impure basic *nickel carbonate* (roughly $2NiCO_3.3Ni(OH)_2.4H_2O$) is obtained as a precipitate when sodium carbonate is added to a solution of a nickel salt. A pure nickel carbonate is prepared by oxidation of nickel powder in ammonia and carbon dioxide (Antonsen, 1981). Nickel carbonate is currently produced by six companies each in the USA and Japan, three each in India and the Federal Republic of Germany, two each in Argentina, France, Italy, Mexico and the UK, and one each in Belgium, Brazil, Canada, Spain and Switzerland (Chemical Information Services Ltd, 1988). Finland and Japan produce the largest volumes of nickel carbonate (ERAMET-SLN, 1989b).

Nickel ammonium sulfate is prepared by reacting nickel sulfate with ammonium sulfate and crystallizing the salt from a water solution (Antonsen, 1981; Sax & Lewis, 1987). Nickel ammonium sulfate (particular form unknown) is currently produced by three companies in the UK, two in the USA and one in Japan (Chemical Information Services, Ltd, 1988).

Nickel chloride (hexahydrate) is prepared by the reaction of nickel powder or nickel oxide with hot aqueous hydrochloric acid (Antonsen, 1981). It is currently produced by eight companies in the USA, six in India, four each in the Federal Republic of Germany, Japan and the UK, three in Mexico, two each in Brazil, France and Italy and one each in Spain, Switzerland and Taiwan (Chemical Information Services Ltd, 1988). The countries or regions that produce the largest volumes are: Czechoslovakia, Federal Republic of Germany, France, Japan, Taiwan, UK, USA and USSR (ERAMET-SLN, 1989b).

Nickel nitrate (anhydrous) can be prepared by the reaction of fuming nitric acid and nickel nitrate hexahydrate. The hexahydrate is prepared by reaction of dilute nitric acid and nickel carbonate (Antonsen, 1981). Nickel nitrate hexahydrate is manufactured on a commercial basis by three methods: (1) slowly adding nickel powder to a stirred mixture of nitric acid and water; (2) a two-tank reactor system, one with solid nickel and one with nitric acid and water; and (3) adding nitric acid to a mixture of black nickel oxide powder and hot water (Antonsen, 1981). Nickel nitrate is currently produced by six companies in the USA, four each in Brazil, Japan and the UK, two each in the Federal Republic of Germany, France, India, Italy and Spain and one each in Argentina, Australia, Belgium, Mexico and Switzerland (Chemical Information Services Ltd, 1988).

Nickel sulfate hexahydrate is made by adding nickel powder or black nickel oxide to hot dilute sulfuric acid or by the reaction of nickel carbonate and dilute sulfuric acid. Large-scale manufacture of the anhydrous form may be achieved by gas-phase reaction of nickel carbonyl with sulfur dioxide and oxygen at 100 °C or in a closed-loop reactor that recovers the solid product in sulfuric acid (Antonsen, 1981).

Nickel sulfate hexa- and heptahydrates are currently produced by nine companies each in Japan and the USA, six in India, four each in Argentina, the Federal Republic of Germany, Mexico and the UK, three in Canada, two each in Austria, Belgium, Brazil and Italy, and one each in Australia, Czechoslovakia, Finland, the German Democratic Republic, Spain, Sweden, Switzerland, Taiwan and the USSR (Chemical Information Services Ltd, 1988). The countries or regions that produce nickel sulfate in the largest volumes are: Belgium, Czechoslovakia, the Federal Republic of Germany, Finland, Japan, Taiwan, the UK, the USA and the USSR (ERAMET-SLN, 1989b).

(*e*) *Other nickel compounds*

Nickel carbonyl can be prepared by the Mond carbonyl process, described above for nickel. Two commercial processes are used to manufacture nickel carbonyl. In the UK, the pure compound is produced by an atmospheric method in which carbon monoxide is passed over freshly reduced nickel. In Canada, high-pressure

carbon monoxide is used in the formation of iron and nickel carbonyl, which are separated by distillation. In the USA, nickel carbonyl was prepared commercially by the reaction of carbon monoxide with nickel sulfate solution (Antonsen, 1981). Nickel carbonyl is currently produced by two companies each in the Federal Republic of Germany and the USA and by one in Japan (Chemical Information Services, Ltd., 1988).

Nickelocene is formed by the reaction of nickel halides with sodium cyclopentadienide (Antonsen, 1981). It is currently produced by two companies in the USA (Chemical Information Services Ltd, 1988).

Nickel selenide (particular form unknown) is produced by one company each in Japan and the USA, *nickel titanate* by one company each in the UK and the USA and *potassium nickelocyanate* by one company each in India and the USA (Chemical Information Services Ltd, 1988).

2.2 Use

Uncharacterized alloys of nickel have been used in tools and weapons since 1200 AD or earlier (Considine, 1974; Tien & Howsen, 1981). In fact, the principal use of nickel has always been in its metallic form combined with other metals and nonmetals as alloys. Nickel alloys are typically characterized by their strength, hardness and resistance to corrosion (Tien & Howsen, 1981). The principal current uses of nickel are in the production of stainless and heat-resistant steels, nonferrous alloys and superalloys. Other major uses of nickel and nickel salts are in electroplating, in catalysts, in the manufacture of alkaline (nickel-cadmium) batteries, in coins, in welding products (coated electrodes, filter wire) and in certain pigments and electronic products (Antonsen, 1981; Tien & Howsen, 1981; Mastromatteo, 1986). Nickel imparts strength and corrosion resistance over a wide range of temperatures and pressures (Sibley, 1985; Chamberlain, 1988).

Worldwide demand for nickel in 1983 was 685 000 tonnes (Sibley, 1985). US consumption of nickel ranged from approximately 93 000 to 122 000 tonnes over the period 1982-86 (Chamberlain, 1988). Table 8 shows the US consumption pattern by end-use for 1983. In 1978, 44% was used in stainless steels and alloy steels, 33% in nonferrous and high-temperature alloys, 17% in electroplating and the remaining 6% primarily as catalysts, in ceramics, in magnets and as salts (Tien & Howson, 1981). In western Europe, it was estimated that, in 1982, 50% of the nickel was used in stainless steels, 10% in alloy steel, 15% in nonferrous alloys, 10% in foundry alloys, 10% in plating and 5% in other applications, such as catalysts and batteries (Eurométaux, 1986).

Table 8. US consumption pattern of nickel in 1983 (%)[a]

Use	Consumption (%)
Transportation	
Aircraft	10.3
Motor vehicles and equipment	10.2
Ship and boat building and repairs	4.3
Chemicals	15.6
Petroleum	8.2
Fabricated metal products	8.8
Electrical	10.7
Household appliances	7.9
Machinery	7.2
Construction	9.7
Other	7.1

[a]From Sibley (1985)

(*a*) *Metallic nickel and nickel alloys*

Pure nickel metal is used to prepare nickel alloys (including steels). It is used as such for plating, electroforming, coinage, electrical components, tanks, catalysts, battery plates, sintered components, magnets and welding rods (Eurométaux, 1986).

Ferronickel is used to prepare steels. Stainless and heat-resistant steels accounted for 93% of its end use in 1986 (Chamberlain, 1988).

Nickel-containing steels with low nickel content (<5% Ni) are used for construction and tool fabrication. Stainless steels are used for general engineering equipment, chemical equipment, domestic applications, hospital equipment, food processing, architectural panels and fasteners, pollution control equipment, cryogenic uses, automotive parts and engine components.

Nickel-copper *alloys* are used for coinage, in industrial piping and valves, marine components, condenser tubes, heat exchangers, architectural trim, thermocouples, desalination plants, ship propellers, etc. Nickel-chromium alloys are used in many high-temperature applications, such as furnaces, jet engine parts and reaction vessels. Molybdenum-containing nickel alloys are notable for their corrosion resistance and thermal stability, as are the nickel-iron-chromium alloys, and are used in nuclear and fossil-fuel steam generators, food-processing equipment and chemical-processing and heat-treating equipment. The majority of permanent magnets are made from nickel-cast iron alloys (Mastromatteo, 1986). The other groups of nickel alloys are used according to their specific properties for acid-resistant equipment, heating elements for furnaces, low-expansion alloys, cryogenic

uses, storage of liquefied gases, high magnetic-permeability alloys and surgical implant prostheses.

(*b*) *Nickel oxides and hydroxides*

The *nickel oxide sinters* are used in the manufacture of alloys, steels and stainless steels (Antonsen, 1981).

Green nickel oxide is used to make nickel catalysts and in the ceramics industry. In specialty ceramics, it is added to frit compositions used for porcelain enamelling of steel; in the manufacture of magnetic nickel-zinc ferrites used in electric motors, antennas and television tube yokes; and as a colourant in glass and ceramic stains used in ceramic tiles, dishes, pottery and sanitary ware (Antonsen, 1981).

Black nickel oxide is used in the manufacture of nickel salts and specialty ceramics. It is also used to enhance the activity of three-way catalysts containing rhodium, platinum and palladium used in automobile exhaust control. Like green nickel oxide, black nickel oxide is also used for nickel catalyst manufacture and in the ceramic industry (Antonsen, 1981).

The major use of *nickel hydroxide* is in the manufacture of nickel-cadmium batteries. It is also used as a catalyst intermediate (Antonsen, 1981).

(*c*) *Nickel sulfides*

Nickel sulfide is used as a catalyst in petrochemical hydrogenation when high concentrations of sulfur are present in the distillates. The major use of nickel monosulfide is as an intermediate in the hydrometallurgical processing of silicate-oxide nickel ores.

(*d*) *Nickel salts*

Nickel acetate is used as a catalyst intermediate, as an intermediate in the formation of other nickel compounds, as a dye mordant, as a sealer for anodized aluminium and in nickel electroplating (Antonsen, 1981).

Nickel carbonate is used in the manufacture of nickel catalysts, in the preparation of coloured glass, in the manufacture of nickel pigments, in the production of nickel oxide and nickel powder, as a neutralizing compound in nickel electroplating solutions, and in the preparation of specialty nickel compounds (Antonsen, 1981).

Nickel ammonium sulfate has limited use as a dye mordant and is used in metal-finishing compositions and as an electrolyte for electroplating (Sax & Lewis, 1987).

Nickel chloride is used as an intermediate in the manufacture of nickel catalysts and to absorb ammonia in industrial gas masks. The hexahydrate is used in nickel electroplating (Antonsen, 1981) and hydrometallurgy (Warner, 1984).

Nickel nitrate hexahydrate is used as an intermediate in the manufacture of nickel catalysts, especially sulfur-sensitive catalysts, and as an intermediate in

loading active mass in nickel-cadmium batteries of the sintered-plate type (Antonsen, 1981).

Nickel sulfate hexahydrate is used as an electrolyte primarily for nickel electroplating and also for nickel electrorefining. It is also used in 'electro-less' nickel plating, as a nickel strike solution for replacement coatings or for nickel flashing on steel that is to be porcelain-enamelled, as an intermediate in the manufacture of other nickel chemicals, such as nickel ammonium sulfate, and as a catalyst intermediate (Antonsen, 1981).

(*e*) *Other nickel compounds*

The primary use for *nickel carbonyl* is as an intermediate in the Mond carbonyl-refining process to produce highly pure nickel. Other uses of nickel carbonyl are in chemical synthesis as a catalyst, as a reactant in carbonylation reactions such as the synthesis of acrylic and methacrylic esters from acetylene and alcohols, in the vapour plating of nickel, and in the fabrication of nickel and nickel alloy components and shapes (Antonsen, 1981; Sax & Lewis, 1987).

Nickelocene is used as a catalyst and complexing agent and *nickel titanate* as a pigment (Sax & Lewis, 1987).

No information was available on the use of *nickel selenides* or *potassium nickelocyanate*.

2.3 Occurrence

(*a*) *Natural occurrence*

Nickel is widely distributed in nature, forming about 0.008% of the earth's crust (0.01% in igneous rocks). It ranks twenty-fourth among the elements in order of abundance (Grandjean, 1984), just above copper, lead and zinc (Mastromatteo, 1986). The core of the earth contains about 8.5% nickel; meteorites have been found to contain 5-50% (National Research Council, 1975). Nickel is also an important constituent of deep–sea nodules, typically comprising about 1.5% (Mastromatteo, 1986). Nickel–containing ores are listed in Table 9.

Laterites are formed by the long-term weathering of igneous rocks which are rich in magnesia and iron and contain about 0.25% nickel. Leaching by acidified groundwater over a long period removes the iron and magnesia, leaving a nickel-enriched residue with nickel contents up to 2.5%. Nickel is found as mixed nickel/iron oxide and as nickel magnesium silicate (garnierite) (Grandjean, 1986; Mastromatteo, 1986). Laterite deposits have been mined in many regions of the world, including New Caledonia, Cuba, the Dominican Republic, Indonesia, the USSR, Greece, Colombia, the Philippines, Guatemala and the USA (Mastromatteo, 1986).

Table 9. Nickel-containing minerals[a]

Name	Chemical composition
Breithauptite	NiSb
Niccolite	NiAs
Zaratite	$NiCO_3 2Ni(OH)_2.4H_2O$
Bunsenite	NiO
Morenosite	$NiSO_4.7H_2O$
Millerite	NiS
Vaesite	NiS_2
Polydomite	Ni_3S_4
Heazlewoodite	Ni_3S_2
Pentlandite	$(Ni,Fe)_9S_8$
Pyrrhotite, nickeliferous	$(Fe,Ni)_{1-x}S$[b]
Garnierite	(Ni, Mg) $SiO_3.nH_2O$

[a]From Grandjean (1986)
[b]From Warner (1984); Grandjean (1986)

Nickel and sulfur combine in a wide range of stoichiometric ratios. Nickel monosulfide (millerite), nickel subsulfide (heazlewoodite), nickel disulfide (vaesite) and Ni_3S_4 (polydymite) are found in mineral form in nature (Considine, 1974). Sulfide nickel ores contain a mixture of metal sulfides, principally pentlandite, chalcopyrite ($CuFeS_2$) and nickeliferous pyrrhotite in varying proportions. The major nickel mineral is pentlandite. While pentlandite may contain about 35% of nickel by weight, the nickel content of pyrrhotite is usually 1% or less, and the sulfide ore available for nickel production generally contains only 1-2% nickel (Grandjean, 1986). A large deposit of pentlandite is located in Sudbury, Ontario, Canada.

Other nickel ores include the nickel-arsenicals and the nickel-antimonials, but these are of much less commercial importance (Mastromatteo, 1986).

(*b*) *Occupational exposures*

Occupational exposure to nickel may occur by skin contact or by inhalation of dusts, fumes or mists containing nickel or by inhalation of gaseous nickel carbonyl. Nickel-containing dusts may also be ingested by nickel workers (Grandjean, 1984). The National Institute for Occupational Safety and Health (1977a) published a list of occupations with potential exposure to nickel (Table 10); it has estimated that about 1.5 million workers in the USA are exposed to nickel and nickel compounds (National Institute for Occupational Safety and Health, 1977b).

Table 10. Occupations with potential exposure to nickel[a]

Battery makers, storage	Mould makers
Catalyst workers	Nickel miners
Cemented carbide makers	Nickel refiners
Ceramic makers	Nickel smelters
Chemists	Nickel workers
Disinfectant makers	Oil hydrogenators
Dyers	Organic chemical synthesizers
Electroplaters	Paint makers
Enamellers	Penpoint makers
Gas-mask makers	Petroleum refinery workers
Ink makers	Spark-plug makers
Jewellers	Stainless-steel makers
Magnet makers	Textile dyers
Metallizers	Vacuum tube makers
Mond process workers	Varnish makers
Nickel-alloy makers	Welders

[a]Adapted from National Institute for Occupational Safety and Health (1977b)

Occupational exposure to nickel is evaluated by monitoring air and blood serum, plasma or urine. (For recent reviews on this subject, see Rigaut, 1983; Grandjean, 1984; Nieboer *et al.*, 1984a; Warner, 1984; Grandjean, 1986; Sunderman *et al.*, 1986a). Tables 11-13 summarize exposure to nickel as measured by air and biological monitoring in various industries and occupations. The biological indicator levels are influenced by the chemical and physical properties of the nickel compound studied and by the time of sampling. It should be noted that the nickel compounds, the timing of collection of biological samples (normally at the end of a shift) and the analytical methods used differ from study to study, and elevated levels of nickel in biological fluids and tissue samples (Table 11) are mentioned only as indications of uptake of nickel, and may not correlate directly to exposure levels (Angerer *et al.*, 1989). (See also section 3.3(*b*) and the monographs on chromium and chromium compounds, and on welding.)

Table 11. Occupational exposure to nickel in the nickel producing industry

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l) (mean ±SD)	Reference
		Mean ±SD	Range	Mean ±SD	Range		
Mines, Ontario (Canada) [1976]		20	6–40				Rigaut (1983)
Mines, Oregon (USA) [1981]		30					Rigaut (1983)
Mines, New Caledonia [1982]		20	6–40				Rigaut (1983)
Smelter, producing ferronickel and matte, New Caledonia		5–76[a]	2–274[b]	< 10 (86% of samples) < 20 (98% of samples)			Warner (1984) Warner (1984)
Laterite mining and smelting, Oregon (USA)[b]							
Ore handling	3	52	5–145				
Drying	4	17	9–21				
Calcining	4	90	37–146				
Skull drilling	8	16	4–43				
Ferrosilicon manufacturing	15	32	4–214				
Mixing	17	6	4–7				
Refining	10	11	4–34				
Handling of finished products	6	5	4–9				
Maintenance	9	39	7–168				
Miscellaneous	3	193	8–420				
Refinery, Clydach (Wales, UK)							Morgan & Rouge (1984)
Kiln							
Before shut-down[c]		310 (26 samples)	10–5000	24±24 (67 samples)		8.9±5.9 (37 samples)	
On return to work[c]				14±7 (20 samples)		3.0±2.0 (20 samples)	

Table 11 (contd)

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l) (mean ±SD)	Reference
		Mean ±SD	Range	Mean ±SD	Range		
Refinery, Clydach (Wales, UK)							
Kiln (contd)							
One month later		190 (30 samples)	10–2890	22±10 (14 samples)		5.5±2.0 (16 samples)	
New powder plant		310 (20 samples)	90–1530				
Before shut-down[c]				37±30 (48 samples)		7.2±4.8 (25 samples)	
On return to work[c]				13±12 (17 samples)		4.0±2.3 (17 samples)	
One month later		500 (22 samples)	50–1810	31±13 (16 samples)		7.6±3.5 (15 samples)	
Old powder plant		1460 (5 samples)	80–5000	33±13 (12 samples)		9.0±3.7 (6 samples)	
Wet-treatment (A)[d]		1540 (8 samples)	220–4180	39±28 (15 samples)		7.4±5.1 (7 samples)	
Wet-treatment (B)[e]		90 (17 samples)	30–150	34±24 (36 samples)		3.4±1.9 (13 samples)	
Refinery, Kristiansand (Norway)[b]							Høgetveit *et al.* (1978)
Roasting–smelting	24	860±1200		65±58		7.2±2.8	
Electrolytic department	90	230±420		129±106		11.9±8.0	
Other processes	13	420±490		45±27		6.4±1.9	

Table 11 (contd)

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l) (mean ±SD)	Reference
		Mean ±SD	Range	Mean ±SD	Range		
Refinery, Kristiansand (Norway)							Torjussen &
Roasting-smelting	97			34±35		5.2±2.7	Andersen (1979)
Electrolysis	144			73±85		8.1±6.0	
Other processes	77			22±18		4.3±2.2	
Electrolytic refinery (USA)	15	489	20–2200	222 124 (μg/g creatinine)	8.6–813 6.1–287		Bernacki *et al.* (1978a)
Electrolytic refinery (FRG)		50		14.8 (μg/g creatinine)	2.5–63		Raithel (1987)
Electrolytic refinery (Czechoslovakia)		600	86–1265	264	125–450		Rigaut (1983)
Hydrometallurgical refinery (Canada)							Warner (1984)
Acid leaching of matte		99	5–1630				
Purification of nickel electrolyte:							
Tube filterman	12	144	13–316				
	12[f]	129	11–316				
Filter pressman	16	209	61–535				
	16[f]	152	31–246				
Filter-press area	11	242	64–508				
	11[f]	221	52–466				

Table 11 (contd)

Industry and activity (country) [year, when available]	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l) (mean ±SD)	Reference
		Mean ±SD	Range	Mean ±SD	Range		
Hydrometallurgical refinery (Canada) (contd)							
Purification of nickel electrolyte[a]:							
Cementation of copper on nickel in Pachuca tanks	39	168	48–644				
	39[f]	38	1–133				
Removal of iron slimes with a tube filter	56	200	27–653				
	56[f]	85	3–433				
Oxidizing cobalt with chlorine	47	183	30–672				
	47[f]	66	1–267				
General operations in a tank house using insoluble anodes	96[a]	336	40–1100				
	45[b]	185	80–400				
Tankhouse using nickel matte anodes:							
General area	11[a]	48	14–223				
	11[a,f]	29	5–210				
Tankman	15[b]	48	18–88				
	15[b,f]	30	12–71				
Anode scrapman	11[b]	179	43–422				
	11[b,f]	52	1–236				

[a]Area air sampling

[b]Personal air sampling

[c]Specimens obtained before and after six months' closure of refinery operations

[d]Short exposures to high levels of insoluble nickel compounds

[e]Chronic exposures to soluble nickel sulfate

[f]Soluble nickel

Table 12. Occupational exposure in industries using primary nickel products

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Reference
		Mean	Range	Mean	Range	
Stainless-steel production						Warner (1984)
Electric furnace shop	8[a]	36	9–65			
Argon–oxygen decarburization	5	35	13–58			
Continuous casting	2	14	11–15			
Grinding/polishing (machine)	6	134	75–189			
Grinding/chipping (hand tool)	2	39	23–48			
Welding, cutting and scarfing[b]	5	111[c]	13–188[c]			
Heat treating	1	54[d]	< 1–104[d]			
Rolling and forging	6	49	< 11–72			
Other operations (maintenance, pickling)	5	58	10–107			
High nickel alloy production (FRG) (a few persons exposed to nickel powder)	59	300[e]		2.6	0.5–52	Raithel (1987)
High nickel alloy production[f]						Warner (1984)
Weighing and melting	369	83[f]	1–4400			
Hot working	153	111	1–4200			
Cold working	504	64	1–2300			
Grinding	96	298	1–2300			
Pickling and cleaning	18	8	1–15			
Maintenance	392	58	1–73			
Production of wrought nickel and alloys *via* metal powder foundries	226	1500[f]	1–60000			Warner (1984)

Table 12 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Reference
		Mean	Range	Mean	Range	
Six jobbing foundries processing alloys containing 0–60% nickel, averaging 10–15% nickel:						Scholz & Holcomb (1980)
Melting	15	21	< 5–62			
Casting	7	14	< 4–35			
Cleaning room:						
Cutting and gouging	11	233	7–900			
Welding	14	94	20–560			
Hand grinding	24	94	< 5–440			
Swing grinding	3	19	13–30			
Jobbing foundry processing carbon, alloy and stainless steel containing 0–10% nickel:						Warner (1984)
Melting and casting	16	13	ND[g]–70			
Cleaning room:						
Air arc gouging	7	310	40–710			
Welding	34	67	10–170			
Three low alloy (0–2% nickel) iron and steel foundries						Warner (1984)
Melting and casting	16	13	4–32			
Cleaning room (grinding, air arc gouging, welding)	18	54	7–156			
Steel foundry (Finland) (steel cutters)	4	518	145–1100	39	18–77	Aitio *et al.* (1985)
Production of soluble nickel salts (Wales, UK)[f]	66 60	500 450	10–20 000 < 10–12 070	(68) 65[h] (60) 49[h]	10–200[h] < 10–210[h]	Morgan & Rouge (1979)

Table 12 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Reference
		Mean	Range	Mean	Range	
Production of nickel salts from nickel or nickel oxide:						Warner (1984)
Nickel sulfate	12	117[f]	9–590			
Nickel chloride	10	196[f,i]	20–485[i]			
Nickel acetate/nitrate	6	155[f]	38–525			

[a]Companies reporting exposures
[b]Samples taken outside protective hood
[c]Excludes one suspiciously high measurement (1460 μg Ni/m³)
[d]Excludes one suspiciously high measurement (500 μg Ni/m³)
[e]The median nickel concentration in workroom air was 300 μg/m³; values that exceeded 500 μg/m³ were found at 2 of 8 measuring stations
[f]Mainly from personal sampling
[g]Not detected
[h]Corrected to 1.6 g/l creatinine
[i]Excludes one suspiciously high value (2780 μg Ni/m³)

Table 13. Occupational exposure in industries using nickel in special applications

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l)		Reference
		Mean	Range	Mean ± SD	Range	Mean	Range	
Ni/Cd-battery production with nickel and nickel hydroxide; assembly and welding of plates	36	378[a,b]	20–1910[a,b]					Warner (1984)
Ni/Cd-battery production (FRG)	51			4.0[c]	1.9–10.9			Raithel (1987)
Ni/Cd or Ni/Zn-battery production (USA)	6			11.7±7.5 10.2	3.4–25 7.2–23 (μg/g creatinine)			Bernacki *et al.* (1978a)
Ni/H_2-battery production	7			32.2±40.4	2.8–103			
Ni/Cd-battery production			12–33		24–27 (μg/g creatinine)			Adamsson *et al.* (1980)
Ni-catalyst production (Netherlands)	73		< 200–5870	64 (μg/g creatinine)	9–300	8	2–41	Zwennis & Franssen (1983)
Ni-catalyst production from nickel sulfate (USA)	7 5	150[a] 370[d]	10–600[a] 190–530[d]					Warner (1984)
Ni-catalyst use; coal gasification workers (USA)	9			4.2 3.2	0.4–7.9 0.1–5.8 (μg/g creatinine)			Bernacki *et al.* (1978a)
Electroplating								Warner (1984)
Sulfate bath, 45°C								
Area 1 sample	16	< 6	< 5–< 8					
Area 2 samples	3	< 4	< 2–< 7					
Personal samples	6	< 11	< 7–< 16					

Table 13 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l)		Reference
		Mean	Range	Mean ± SD	Range	Mean	Range	
Electroplating (contd)								
Sulfate bath, 70°C								
Area samples	6	< 3	< 2–< 3					
Sulfamate bath, 45–55°C								
Area 1 sample	9	< 4	< 4					
Area 2 samples	6	< 4	< 4					
Electroplating (Finland)		90	20–170	53.5	12–109	6.1	1.2–14.1	Tossavainen *et al.* (1980)
Electroplating (Finland)		–	30–160	–	25–120	–	3–14	Tola *et al.* (1979)
Electroplating (USA)		9.3[a]	0.5–21.2	48	5–262			Bernacki *et al.* (1980)
Electroplating (USA)	21			30.4 (21.0	3.6–85 2.4–62 μg/g creatinine)			Bernacki *et al.* (1978a)
Electroplating (India)	12			12.2	11–26			Tandon *et al.* (1977)
Electroplating (FRG)		10 (soluble anode)						Gross (1987)
		110 (insoluble anode)						
		7 (insoluble anode and wetting agent)			1.7–3.6			
Exposed persons in the hollow glass industry (FRG)	9		3–3800	11.9 (946 samples)	3.6–42.1[e]	1.6	0.75–3.25[e] (288 samples)	Raithel (1987)
Flame sprayer			3–600	25.3 (114 samples)	8.5–81.5	1.95	0.75–3.25 (40 samples)	

Table 13 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l)		Reference
		Mean	Range	Mean ± SD	Range	Mean	Range	
Grinder, polisher			18–3800	7.4 (406 samples)	2.9–24.3	0.9	0.75–2.05 (140 samples)	
Mixed mechanical work and flame spraying			300–410	17.5 (394 samples)	4.9–53.9	1.65	0.75–4.10 (108 samples)	
Plasma spraying (FRG)	6	200			3.4–12.5			Gross (1987)
Spark eroding (FRG)	6	< 10			0.7–2.1			Gross (1987)
Flame spraying (USA)	5	2.4	< 1–6.5	17.2 (16.0	1.4–26 1.4–54 μg/g creatinine)			Bernacki *et al.* (1978a)
Plasma cutting (FRG)	17		< 100		1.1–6.5			Gross (1987)
Painting								
Spray painting in a construction shipyard (USA)	13			3.2	< 0.5–9.2	4.4	< 0.5–17.2	Grandjean *et al.* (1980)
Painting in repair shipyard (USA)	18					5.9	< 0.5–13	Grandjean *et al.* (1980)
Manufacturing paints (USA)	10			15.3±11.1	6–39			Tandon *et al.* (1977)
Buffing, polishing, grinding								
Buffers and polishers (aircraft engine factory) (USA)	7	26	< 1–129	4.1 (2.4	0.5–9.5 0.5–4.7 μg/g creatinine)			Bernacki *et al.* (1978a)
Grinders (abrasive wheel grinding of aircraft parts) (USA)	9	1.6	< 1–9.5	5.4 (3.5	2.1–8.8 1.7–6.1 μg/g creatinine)			Bernacki *et al.* (1978a)

Table 13 (contd)

Industry and activity (country)	No. of workers	Air (μg/m³)		Urine (μg/l)		Serum (μg/l)		Reference
		Mean	Range	Mean ± SD	Range	Mean	Range	
Polisher, grinder (FRG)	15	140			0.7–9.9			Gross (1987)
Polisher, grinder (stainless steel) (FRG)	46	350[c]	10–10 000[f]	28	(12) 3–7[l]			Heidermanns *et al.* (1983)
Miscellaneous exposure								
Bench mechanics (assembling, fittings and finishing aircraft parts made of Ni-alloys) (USA)	8	52	< 1–252	12.2 (7.2	1.4–41 0.7–20 μg/g creatinine)			Bernacki *et al.* (1978a)
Riggers/carpenters (construction shipyard) (USA)	16			3.7	1.1–13.5	3.3	1.1–13.5	Grandjean *et al.* (1980)
Riggers/carpenters (repair shipyard) (USA)	11					3.6	< 0.5–7.4	Grandjean *et al.* (1980)
Shipfitters/pipefitters (construction shipyard (USA)	6			4.9	3.7–7.1	4.1	1.5–6.8	Grandjean *et al.* (1980)
Shipfitters/pipefitters (repair shipyard) (USA)	15					9.1	0.5–3.8	Grandjean *et al.* (1980)

[a]Personal air sampling

[b]Excludes three suspiciously high values (5320; 18 300; 53 300 μg/m³)

[c]Median

[d]Area air monitoring

[e]68th percentile range

[f]90th percentile range

(i) *Nickel mining and ore comminution*

On the basis of personal gravimetric sampling among Canadian underground miners of nickel, the time-weighted average concentration of total airborne nickel was about 25 μg/m³ and that of respirable nickel, < 5 μg/m³ (see Table 11; Warner, 1984). Ore miners may also be exposed to radon, oil mist, diesel exhausts and asbestos (see IARC, 1977, 1988a, 1989).

(ii) *Nickel roasting, calcining, smelting and refining*

The nickel content of air samples from a Sudbury (Canada) smelter seldom exceeded 0.5 mg/m³ but could be as high as 1 mg/m³. The average concentrations of airborne nickel were higher in the roaster areas (0.048 mg/m³) than in the converter areas (0.033 mg/m³), because the handling of fine solids is a greater source of dust than the handling of molten phases. Thus, work-place air may contain roaster feed and product, which include various nickel-containing minerals and solid solutions of nickel in iron oxides. Nickel-bearing dusts from converters contain mainly nickel subsulfide (Warner, 1984). Arsenic, silica, copper, cobalt and other metal compounds may also occur in work-place air.

Emissions from the high-temperature ore calcining and smelting furnaces used to produce ferronickel from lateritic ores would contain nickel predominantly in the form of silicate oxides and iron-nickel mixed/complex oxides of the ferrite or spinel type. The nickel content of these dusts can range from 1 to 10% (International Committee on Nickel Carcinogenesis in Man, 1990).

Average concentrations of airborne nickel in refining operations can be considerably higher than those encountered in mining and smelting because of the higher nickel content of the materials being handled in the refining process (Table 11). The nickel species that may be present in various refining operations include nickel subsulfide, nickel monoxide, nickel-copper oxides, nickel-iron oxides, metallic nickel, pure and alloyed, nickel sulfate, nickel chloride and nickel carbonate. Other possible exposures would be to hydrogen sulfide, ammonia, chlorine, sulfur dioxide, arsenic and polycyclic aromatic hydrocarbons (Warner, 1984; International Committee on Nickel Carcinogenesis in Man, 1990).

A recent attempt has been made, in conjunction with a large epidemiological study (International Committee on Nickel Carcinogenesis in Man, 1990), to estimate past exposures in various nickel refineries using different processes. Exposure estimates were made first for total airborne nickel, based either on historical measurements (after 1950) or on extrapolation of recent measurements. In all cases, further estimates were made of nickel species (metallic, oxidic, sulfidic and soluble), as defined in the report, on the basis of knowledge of the processes and rough estimates of the ratio of the various species generated in each process.

Prior to the widespread use of personal samplers, high-volume samplers were used to take area samples; however, in many instances, neither personal gravimetric nor high-volume samples were available, and konimeter readings were the only available means of assessing the level of airborne dust. No measurement of the actual concentration of nickel, and especially nickel species, in work places exists for any refining operation prior to 1950. More recently, measurements have been made of total dust and, in some cases, total nickel content of dust or mist in refinery work-place air. Conversion of high-volume sampler and konimeter measurements to concentrations comparable to personal gravimetric sampler measurements introduces another uncertainty in the environmental estimates. The main reason for this uncertainty is that it is impossible to derive unique conversion factors to interrelate measurements from the three devices; different particle size distributions give rise to different conversion factors. Information concerning particle size in airborne dusts was seldom available in the work places under study (International Committee on Nickel Carcinogenesis in Man, 1990).

Estimates of nickel exposure were further divided into four categories representing different nickel species: (i) metallic nickel, (ii) oxidic nickel [undefined, but generally understood to include nickel oxide combined with various other metal oxides, such as iron, cobalt and copper oxides], (iii) sulfidic nickel (including nickel subsulfide) and (iv) soluble nickel, defined as consisting 'primarily of nickel sulfate and nickel chloride but may in some estimates include the less soluble nickel carbonate and nickel hydroxide'. No actual measurement of specific nickel species in work-place air was available upon which to base exposure estimates. As a result, the estimates are necessarily very approximate. This is clear, for example, from the estimates for linear calciners at the Clydach refinery (Wales, UK), which gave total nickel concentrations of 10-100 mg/m^3, with 0-5% soluble nickel. Because of the inherent error in the processes of measurement and speciation and the uncertainty associated with extrapolating estimates from recent periods to earlier periods, the estimated concentrations of nickel species in work places in this study (International Committee on Nickel Carcinogenesis in Man, 1990) must be interpreted as broad ranges indicating only estimates of the order of magnitude of the actual exposures.

(iii) *Production of stainless steel and nickel alloys*

While some stainless steels contain up to 25-30% nickel, nearly half of that produced contains only 8-10% nickel. Nickel oxide sinter is used as raw material for stainless and alloy steelmaking in some plants, and oxidized nickel may be found in the fumes from many melting/casting and arc/torch operations in the melting trades. The nickel concentrations in air in the stainless and alloy producing industries were given in Table 12. Occupational exposure in alloy steel making should generally be lower than those observed for comparable operations with stainless

steel. The normal range of nickel in alloy steels is 0.3-5% but the nickel content can be as high as 18% for certain high-strength steels. The production of 'high nickel' alloys consumes about 80% of the nickel used for nonferrous applications. The technology is very similar to that used for stainless steel production except that melting and decarburizing units are generally smaller and greater use is made of vacuum melting and remelting. Since these alloys contain more nickel than stainless and alloy steels, the concentrations of nickel in workroom air are generally higher than for comparable operations with stainless and alloy steels (Warner, 1984).

(iv) *Steel foundries*

In foundries, shapes are cast from a wide variety of nickel-containing materials. Melts ranging in size from 0.5 to 45 tonnes are prepared in electric arc or induction furnaces and cast into moulds made of sand, metal or ceramic. The castings are further processed by chipping and grinding and may be repaired by air arc gouging and welding. Foundry operations can thus be divided roughly into melting/casting and cleaning room operations. Typical levels of airborne nickel in steel foundries were presented in Table 12 (Warner, 1984). Health hazards in foundry operations include exposure to silica and metal fumes and to degradation products from moulds and cores, such as carbon monoxide, formaldehyde and polycyclic aromatic hydrocarbons (see IARC, 1984).

(v) *Production of nickel-containing batteries*

The principal commercial product in nickel-containing batteries is the electrochemical couple nickel/cadmium. Other couples that have been used include nickel/iron, nickel/hydrogen and nickel/zinc. In nickel-cadmium batteries, the positive electrode is primarily nickel hydroxide, contained in porous plates. The positive material is made from a slurry of nickel hydroxide, cobalt sulfate and sodium hydroxide, dried and ground with graphite flake. Sintered nickel plates impregnated with the slurry may also be used. The nickel/hydrogen system requires a noble metal catalyst and operates at high pressures, requiring a steel pressure vessel. Nickel/iron batteries can be produced using nickel foil (Malcolm, 1983).

The concentrations of nickel in air and in biological samples from workers in the nickel-cadmium battery industry were summarized in Table 13. Workers in such plants are also exposed to cadmium.

(vi) *Production and use of nickel catalysts*

Metallic nickel is used as a catalyst, often alloyed with copper, cobalt or iron, for hydrogenation and reforming processes and for the methane conversion and Fischer-Tropsch reactions. Mixed, nickel-containing oxides are used as partial oxidation catalysts and as hydrodesulfuration catalysts (cobalt nickel molybdate) (Gentry *et al.*, 1983). Occupational exposure occurs typically in the production of

catalysts from metallic nickel powder and nickel salts such as nickel sulfate (Warner, 1984), but coal gasification process workers who use Raney nickel as a hydrogenation catalyst have also been reported to be exposed to nickel (Bernacki *et al.*, 1978a). Exposure levels are generally higher in catalyst production than during the use of catalysts (see Table 13).

(vii) *Nickel plating*

Metal plating is an operation whereby a metal, commonly nickel, is deposited on a substrate for protection or decoration purposes. Nickel plating can be performed by electrolytic processes (electroplating) or 'electroless' processes (chemical plating), with aqueous solutions (the 'baths'). During electroplating, nickel is taken out of the solution and deposited on the substrate, which acts as the cathode. Either soluble anodes, made from metallic nickel feed, or insoluble anodes, in which the nickel is introduced as the hydroxycarbonate, are used. The baths contain a mixture of nickel sulfate and/or chloride or, less often, sulfamate. In electroless processes, a hypophosphite medium is used, the nickel feed being nickel sulfate.

The electrolyte contains soluble nickel salts, such as nickel fluoborate, nickel sulfate and nickel sulfamate (Warner, 1984). Nickel plating can be performed with a soluble (metallic nickel) or insoluble anode. The principal source of air contamination in electroplating operations is release of the bath electrolyte into the air. Electroplaters are exposed to readily absorbed soluble nickel salts by inhalation, which subsequently causes high levels in urine (Tola *et al.*, 1979; see Table 13).

(viii) *Welding*

Welding produces particulate fumes that have a chemical composition reflecting the elemental content of the consumable used. For each couple of process/material of application, there is a wide range of concentrations of elements present in the fume. Nickel and chromium are found in significant concentrations in fumes from welding by manual metal arc, metal inert gas and tungsten inert gas processes on stainless and alloy steels. Typical ranges of total fume and nickel, as found in the breathing zone of welders, are presented in Table 14. Certain special process applications not listed can also produce high nickel and chromium concentrations, and manual metal arc and metal inert gas welding of nickel in confined spaces produce significantly higher concentrations of total fume and elemental constituents. Exposure to welding fumes that contain nickel and chromium can lead to elevated levels of these elements in tissues, blood and urine (see monograph on welding for details).

(ix) *Thermal spraying of nickel*

Thermal spraying of nickel is usually performed by flame spraying or plasma spraying (Gross, 1987). For flame spraying, nickel in wire form is fed to a gun

Table 14. Total fume and nickel concentrations found in the breathing zone of welders[a]

Process[b]	Total fume[c] (mg/m³)	Ni (μg/m³)
MMA/SS	4-10	10-1000
MIG/SS	2-5	30-500
TIG/SS	2-6	10-40

[a]Compiled from Table 4 of monograph on welding
[b]MMA, manual metal arc; SS, stainless steel; MIG, metal inert gas; TIG, tungsten inert gas
[c]50-90% range

fuelled by a combustible gas such as acetylene, propane or natural gas. The wire is melted in the oxygen-fuel flame, atomized with compressed air, and propelled from the torch at velocities up to 120 m/s. The material bonds to the workpiece by a combination of mechanical interlocking of the molten particles and a cementation of partially oxidized material.

The material can also be sprayed in powder form, the fuel gases being either acetylene or hydrogen and oxygen. The powder is aspirated by an air stream, and the molten particles are deposited on the workpiece with high efficiency. For plasma spraying, an electric arc is established in the controlled atmosphere of a special nozzle. Argon is passed through the arc, where it ionizes to form a plasma that continues through the nozzle and recombines to create temperatures as high as 16 700 °C. Powder is melted in the stream and released from the gun at a velocity of approximately 10 m/s (Burgess, 1981; Pfeiffer & Willert, 1986).

Workers who construct or repair nickel-armoured moulds in hollow-glass and ceramics factories use flame spraying with metallic powder (70-98% Ni) and are exposed to nickel dusts (as metallic and oxidic nickel) and fumes. After the moulds have been polished with grinding discs, abrasives and emery paper, they are installed in glass-making machines. Exposure levels in various types of thermal spraying, cutting and eroding were shown in Table 13.

(x) *Production and use of paints*

Some pigments for paints (e.g., nickel flake) and colours for enamels (e.g., nickel oxide) contain nickel. Exposure to nickel can occur when spraying techniques are used and when the paints are manufactured (Tandon *et al.*, 1977; Mathur & Tandon, 1981). Paint and pigment workers have slightly higher concentrations of nickel in plasma and urine than controls (see Table 13). Sandblasters may be exposed to

dusts from old paints containing nickel and, additionally, to nickel-containing abrasive materials (Stettler *et al.*, 1982).

(xi) *Grinding, polishing and buffing of nickel-containing metals*

Grinding, polishing and buffing involve controlled use of bonded abrasives for metal finishing operations; in many cases the three operations are conducted in sequence (for review, see Burgess, 1981). Grinding includes cutting operations in foundries for removal of gates, sprues and risers, rough grinding of forgings and castings, facing off of welded assemblies and grinding out major surface imperfections. Grinding is done with wheels made of selected abrasives in bonding structural matrices. The commonly used abrasives are aluminium oxide and silicon carbide. The wheel components normally make up only a small fraction of the total airborne particulates released during grinding, and the bulk of the particles arise from the workpiece. Polishing techniques are used to remove workpiece surface imperfections such as tool marks, and this may remove as much as 0.1 mm of stock from a workpiece. In buffing, little metal is removed from the workpiece, and the process merely provides a high lustre surface by smearing any surface roughness with a high weight abrasive; e.g., ferric oxide and chromium oxide are used for soft metals, aluminium oxide for harder metals. Sources of airborne contaminants from grinding, polishing and buffing have been identified (Burgess, 1981; König *et al.*, 1985). Grinding, polishing and buffing cause exposures to metallic nickel and to nickel-containing alloys and steels (see Table 13).

(xii) *Miscellaneous exposure to nickel*

A group of employees exposed to metallic nickel dust was identified among employees of the Oak Ridge Gaseous Diffusion Plant in the USA. In one department, finely-divided, highly pure, nickel powder was used to manufacture 'barrier', a special porous medium employed in the isotope enrichment of uranium by gaseous diffusion. The metallic powder was not oxidized during processing. Routine air sampling was performed at the plant from 1948 to 1963, during which time 3044 air samples were collected in seven areas of the barrier plant and analysed for nickel content. The median nickel concentration was 0.13 mg/m^3 (range, $<$0.1-566 mg/m^3), but the authors acknowledged that the median exposures were probably underestimated (Godbold & Tompkins, 1979). Other determinations of nickel in miscellaneous industries and activities were presented in Table 13.

(*c*) *Air*

Nickel enters the atmosphere from natural sources (e.g., volcanic emissions and windblown dusts produced by weathering of rocks and soils), from combustion of fossil fuels in stationary and mobile power sources, from emissions from nickel mining and refining operations, from the use of metals in industrial processes and

from incineration of wastes (Sunderman, 1986a; US Environmental Protection Agency, 1986). The estimated global emission rates are given in Table 15. The predominant forms of nickel in the ambient air appear to be nickel sulfate and complex oxides of nickel with other metals (US Environmental Protection Agency, 1986).

Table 15. Emission of nickel into the global atmosphere[a]

Source	Emission rate (10^6 kg/year)
Natural	
Wind-blown dusts	4.8
Volcanoes	2.5
Vegetation	0.8
Forest fires	0.2
Meteoric dusts	0.2
Sea spray	0.009
Total	8.5
Anthropogenic[b]	
Residual and fuel oil combustion	27
Nickel mining and refining	7.2
Waste incineration	5.1
Steel production	1.2
Industrial applications	1.0
Gasoline and diesel fuel combustion	0.9
Coal combustion	0.7
Total	43.1

[a]From Bennett (1984)
[b]Emissions during the mid-1970s

Nickel concentrations in the atmosphere at remote locations were about 1 ng/m³ (Grandjean, 1984). Ambient levels of nickel in air ranged from 5 to 35 ng/m³ at rural and urban sites (Bennett, 1984). Surveys have indicated wide variations but no overall trend. In the USA, atmospheric nickel concentrations averaged 6 ng/m³ in nonurban areas and 17 ng/m³ (in summer) and 25 ng/m³ (in winter) in urban areas (National Research Council, 1975). Salmon *et al.* (1978) reported nickel concentrations in 1957-74 at a semirural site in England to range from 10 to 50 ng/m³ (mean, 19 ng/m³). Nickel concentrations at seven sites in the UK ranged, with one exception, from <2 to 4.8 ng/kg [<2.5 to 5.9 ng/m³] (Cawse, 1978). Annual averages in four Belgian cities were 9-60 ng/m³ during 1972-77 (Kretzschmar *et al.*, 1980). Diffuse sources (traffic, home heating, distant sources) generally predominated.

High levels of nickel in air (110-180 ng/m³) were recorded in heavily industrialized areas and larger cities (Bennett, 1984).

Local airborne concentrations of nickel are high around locations where nickel is mined (e.g., 580 ng/m³ in Ontario, Canada) (McNeely *et al.*, 1972). The average atmospheric nickel concentration near a nickel refinery in West Virginia (USA) was 1200 ng/m³, compared to 40 ng/m³ at six sampling stations not contiguous to the nickel plant. The highest concentration on a single day was about 2000 ng/m³ near a large nickel production facility (Grandjean, 1984).

Average exposure to nickel by inhalation has been estimated to be 0.4 μg/day (range, 0.2-1.0 μg/day) for urban dwellers and 0.2 μg/day (range, 0.1-0.4 μg/day) for rural dwellers (Bennett, 1984).

(*d*) *Tobacco smoke*

Cigarette smoking can cause a daily absorption of nickel of 1 μg/pack due to the nickel content of tobacco (Grandjean, 1984). Sunderman and Sunderman (1961) and Szadkowski *et al.* (1969) found average nickel contents of 2.2 and 2.3 μg/cigarette, respectively, with a range of 1.1-3.1. The latter authors also showed that 10-20% of the nickel in cigarettes is released in mainstream smoke; most of the nickel was in the gaseous phase. The nickel content of mainstream smoke ranges from 0.005 to 0.08 μg/cigarette (Klus & Kuhn, 1982). It is not yet known in what form nickel occurs in mainstream smoke (US Environmental Protection Agency, 1986); it has been speculated that it may be present as nickel carbonyl (Grandjean, 1984), but, if so, it must occur at concentrations of < 0.1 ppm (Alexander *et al.*, 1983). Pipe tobacco, cigars and snuff have been reported to contain nickel at levels of the same magnitude (2-3 μg/g tobacco) (National Research Council, 1975).

(*e*) *Water and beverages*

Nickel enters groundwater and surface water by dissolution of rocks and soils, from biological cycles, from atmospheric fallout, and especially from industrial processes and waste disposal, and occurs usually as nickel ion in the aquatic environment. Most nickel compounds are relatively soluble in water at pH values less than 6.5, whereas nickel exists predominantly as nickel hydroxides at pH values exceeding 6.7. Therefore, acid rain has a pronounced tendency to mobilize nickel from soil and to increase nickel concentrations in groundwater.

The nickel content of groundwater is normally below 20 μg/l (US Environmental Protection Agency, 1986), and the levels appear to be similar in raw, treated and distributed municipal water. In US drinking-water, 97% of all samples ($n = 2503$) contained $\leq$20 μg/l, while about 90% had $\leq$10 μg/l (National Research Council, 1975). Unusually high levels were found in groundwater polluted with soluble nickel compounds from a nickel-plating facility (up to 2500 μg/l) and in water from 12

wells (median, 180 μg/l) (Grandjean, 1984). The median level in Canadian groundwater was <2 μg/l, but high levels were reported in Ontario (Méranger *et al.*, 1981). In municipal tap-water near large open-pit nickel mines, the average nickel concentration was about 200 μg/l, while that in a control area had an average level of about 1 μg/l (McNeely *et al.*, 1972).

Nickel concentrations in drinking-water in European countries were reported to range in general from 2-13 μg/l (mean, 6 μg/l) (Amavis *et al.*, 1976). Other studies have suggested low background levels in drinking-water, e.g., in Finland an average of about 1 μg/l (Punsar *et al.*, 1975) and in Italy mostly below 10 μg/l. In the German Democratic Republic, drinking-water from groundwater showed an average level of 10 μg/l nickel, slightly below the amount present in surface water (Grandjean, 1984). In the Federal Republic of Germany, the mean concentration of nickel in drinking-water was 9 μg/l, with a maximal value of 34 μg/l (Scheller *et al.*, 1988).

The nickel concentration in seawater ranges from 0.1 to 0.5 μg/l, whereas the average level in surface waters is 15-20 μg/l. Freshly fallen arctic snow was reported to contain 0.02 μg/kg, a level that represents 5–10% of those in annual condensed layers (Mart, 1983).

Nickel concentrations of 100 μg/l have been found in wine; average levels of about 30 μg/l were measured in beer and levels of a few micrograms per litre in mineral water (Grandjean, 1984). In the Federal Republic of Germany, however, the mean concentration of nickel in mineral waters was 10 μg/l, with a maximal value of 31 μg/l (Scheller *et al.*, 1988).

(f) *Soil*

The nickel content of soil may vary widely, depending on mineral composition: a normal range of nickel in cultivated soils is 5-500 μg/g, with a typical level of 50 μg/g (National Research Council, 1975). In an extensive survey of soils in England and Wales, nickel concentrations were generally 4-80 μg/g (median, 26 μg/g; maximum, 228 μg/g) (Archer, 1980). Farm soils from different parts of the world contained 3-1000 μg/g. Nickel may be added to agricultural soils by application of sewage sludge (National Research Council, 1975).

The nickel content of coal was 4-24 μg/g, whereas crude oils (especially those from Angola, Colombia and California) contained up to 100 μg/g (Tissot & Weltle, 1984; World Health Organization, 1990).

(g) *Food*

Nickel levels in various foods have been summarized recently (Grandjean, 1984; Smart & Sherlock, 1987; Scheller *et al.*, 1988; Grandjean *et al.*, 1989). Table 16 gives the results of analyses for nickel in various foodstuffs in Denmark; the mean level of nickel in meat, fruit and vegetables was ≤0.2 mg/kg fresh weight. This result was confirmed by analysis of hundreds of food samples from Denmark, the Federal Republic of Germany and the UK (Nielsen & Flyvholm, 1984; Veien & Andersen, 1986; Smart & Sherlock, 1987; Scheller *et al.*, 1988): the nickel content of most samples was < 0.5 mg/kg. The nickel concentration in nuts was up to 3 mg/kg (Veien & Andersen, 1986) and that in cocoa up to 10 mg/kg (Nielsen & Flyvholm, 1984). The nickel content of wholemeal flour and bread was significantly higher than that of more refined products due to the high nickel content of wheat germ (Smart & Sherlock, 1987). High nickel levels in flour may also originate from contamination during milling. In addition, fats can contain nickel, probably owing to the use of nickel catalysts in commercial hydrogenation. Margarine normally contains less than 0.2 mg/kg, but levels up to 6 mg/kg have been found (Grandjean, 1984).

Table 16. Nickel content (mg/kg) in foods in the average Danish diet[a]

Food	No. of samples	Range	Mean
Milk products			
Full milk	63	BDL[b]-0.13	0.02
Yogurt	3	0.004-0.03	0.01
Cream	3	0.01-0.04	0.03
Cheese	25	0.02-0.34	0.10
Meat, fish, eggs			
Beef	32	0.01-0.03	0.02
Pork	20	< 0.02-0.02	0.02
Chicken	9	0.02-0.24	0.11
Lamb	12	< 0.02-0.02	0.02
Liver, kidney	108	0-0.94	0.11
Fish	658	0.005-0.303	0.04
Egg	30	0.01-0.35	0.05
Roots and vegetables			
Potatoes	45	BDL-0.44	0.14
Carrots	17	< 0.01-0.16	0.04
Celery root	8	0.04-0.1	0.06
Beetroot	7	0.01-0.3	0.12
Cabbage	31	0.01-0.63	0.17
Cauliflower	5	0.03-1.0	0.3

Table 16 (contd)

Food	No. of samples	Range	Mean
Roots and vegetables (contd)			
Kale	2	0.15-0.24	0.20
Lettuce	21	BDL-1.4	0.36
Spinach	15	0.02-2.99	0.52
Asparagus	1	-	0.42
Cucumber	8	0.01-0.11	0.04
Tomatoes	21	0.01-0.25	0.07
Peas	24	0.13-0.8	0.42
Fruits			
Apples	11	BDL-0.03	0.01
Pears	10	0.07-0.42	0.14
Plums	10	0.03-0.20	0.12
Currants	13	0.01-0.2	0.06
Strawberries	9	0.03-0.08	0.05
Rhubarb	10	0.01-0.22	0.13
Grapes	4	0.01-0.04	0.02
Raisins	3	0.02-0.04	0.03
Citrus fruits	3	0.01-0.04	0.03
Bananas	4	0.01-0.03	0.02
Canned fruits	65	0.02-1.36	0.31
Juice	11	0.01-0.17	0.04
Meal, grain and bread			
Wheat flour	32	0.03-0.3	0.13
Rye flour	15	0.03-0.3	0.1
Oatmeal	18	0.80-4.7	1.76
Rice	16	0.08-0.45	0.21
Other			
Butter	4	0.03-0.2	0.1
Margarine	13	0.2-2.5	0.34
Sugar	22	0.01-0.09	0.05

[a]From Grandjean *et al.* (1989)
[b]BDL, below detection limit [not specified]

Stainless-steel kitchen utensils have been shown to release nickel into acid solutions, especially during boiling (Christensen & Möller, 1978). The amount of nickel liberated depends on the composition of the utensil, the pH of the food and the length of contact. The average contribution of kitchen utensils to the oral intake of nickel is unknown, but they could augment alimentary exposure by as much as 1 mg/day (Grandjean *et al.*, 1989).

A study of hospital diets in the USA showed that the general diet contained 160 μg/day, and special diets varied by less than 40% from this level (Myron *et al.*, 1978). A recent study (Nielsen & Flyvholm, 1984) suggested a daily intake of 150 μg in the average Danish diet. Knutti and Zimmerli (1985) found dietary intakes in Switzerland of 73 ± 9 μg in a restaurant, 83 ± 9 μg in a hospital, 141 + 33 μg in a vegetarian restaurant and 142 ± 20 μg in a military canteen. The mean nickel intake in the UK in 1981-84 was 140-150 μg/day (Smart & Sherlock, 1987).

(*h*) *Humans tissues and secretions*

The estimated average body burden of nickel in adults is 0.5 mg/70 kg (7.4 μg/kg bw). In post-mortem tissue samples from adults with no occupational or iatrogenic exposure to nickel compounds, the highest nickel concentrations were found in lung, bone, thyroid and adrenals, followed by kidney, heart, liver, brain, spleen and pancreas in diminishing order (Seemann *et al.*, 1985; Sunderman, 1986b; Raithel, 1987; Raithel *et al.*, 1987; Rezuke *et al.*, 1987; Kollmeier *et al.*, 1988; Raithel *et al.*, 1988). Reference values for nickel concentrations in autopsy tissues from nonexposed persons are listed in Table 17.

The mean nickel concentration in lung tissues from 39 nickel refinery workers autopsied during 1978-84 was 150 (1-1344) μg/g dry weight. Workers employed in the roasting and smelting department had an average nickel concentration of 333 (7-1344) μg/g, and those who had worked in the electrolysis department had an average nickel concentration of 34 (1-216) μg/g dry weight. Lung tissue from 16 persons who were not connected with the refinery contained an average level of 0.76 (0.39-1.70) μg/g dry weight (Andersen & Svenes, 1989).

The concentrations of nickel in body fluids have diminished substantially over the past ten years as a consequence of improved analytical techniques, including better procedures to minimize nickel contamination during collection and assay. Concentrations of nickel in human body fluids and faeces are given in Table 18 (see also Sunderman, 1986b; Sunderman *et al.*, 1986a).

(*i*) *Iatrogenic exposures*

Potential iatrogenic sources of exposure to nickel are dialysis treatment, leaching of nickel from nickel-containing alloys used as prostheses and implants and contaminated intravenous medications (for review, see Grandjean, 1984; Sunderman *et al.*, 1986a).

Table 17. Concentrations of nickel in human autopsy tissues

Tissue	No. of subjects	Nickel concentration				Reference
		ng/g wet weight		ng/g dry weight		
		Mean±SD	Range	Mean±SD	Range	
Lung	4	16 ± 8	8-24	86 ± 56	33-146	Rezuke *et al.* (1987)
	8	119 ± 50	48-221	-	-	
	9	-	-	132 ± 99	50-290	
	41	7 ± 10	< 1-70	-	-	
	9	18 ± 12	7-46	173 ± 94	71-371	
	15	-	-	180 ± 105	43-361	Seemann *et al.* (1985)
	70	137 ± 187	-	754 ± 1010	-	Kollmeier *et al.* (1988)
	30	20-40[a]	8-120[a]	107-195[a]	42-600[a]	Raithel *et al.* (1988)
	16	-	-	760 ± 390	390-1700	Andersen & Svenes (1989)
Kidney	8	11 ± 4	7-15	-	-	Rezuke *et al.* (1987)
	6	-	-	125 ± 54	50-120	
	36	14 ± 27	< 1-165	-	-	
	10	9 ± 6	3-25	62 ± 43	19-171	
	18	-	-	34 ± 22	< 5-84	Seemann *et al.* (1985)
Liver	4	9 ± 3	5-13	32 ± 12	21-48	Rezuke *et al.* (1987)
	8	8 ± 2	6-11	-	-	
	10	10 ± 7	8-21	50 ± 31	11-102	
	23	-	-	18 ± 21	< 5-86	Seemann *et al.* (1985)
Heart	4	6 ± 2	4-8	23 ± 6	16-30	Rezuke *et al.* (1987)
	8	7 ± 2	4-9	-	-	
	9	8 ± 5	1-14	54 ± 40	10-110	
Spleen	22	-	-	23 ± 20	< 5-85	Seemann *et al.* (1985)
	10	7 ± 5	1-15	37 ± 31	9-95	Rezuke *et al.* (1987)

[a]Range of median values and 68th percentile of range on the basis of 600 lung specimens from 30 autopsies

Table 18. Nickel concentrations in specimens from healthy, unexposed adults[a]

Specimen	Mean ± SD	Range	Units
Whole blood	0.34 ± 0.28	< 0.05-1.05	µg/l
Serum	0.28 ± 0.24	< 0.05-1.08	µg/l
Urine (spot collection)	2.0 ± 1.5	0.5-6.1	µg/l
	2.0 ± 1.5	0.4-6.0	µg/g creatinine
	2.8 ± 1.9	0.5-8.8	µg/l[b]
Urine (24-h collection)	2.2 ± 1.2	0.7-5.2	µg/l
	2.6 ± 1.4	0.5-6.4	µg/day
Faeces (3-day collection)	14.2 ± 2.7	10.8-18.7	µg/g (dry weight)
	258 ± 126	80-540	µg/day

[a]From Sunderman *et al.* (1986a)
[b]Factored to specific gravity = 1.024

Hypernickelaemia has been observed in patients with chronic renal disease who are maintained by extracorporeal haemodialysis or peritoneal dialysis (Table 19; Linden *et al.*, 1984; Drazniowsky *et al.*, 1985; Hopfer *et al.*, 1985; Savory *et al.*, 1985; Wills *et al.*, 1985). In one severe incident, water from a nickel-plated stainless-steel water-heater contaminated the dialysate to approximately 250 µg/l, resulting in plasma nickel levels of 3000 µg/l and acute nickel toxicity (Webster *et al.*, 1980). Even during normal operation, the average intravenous uptake of nickel may be 100 µg per dialysis (Sunderman, 1983a).

Nickel-containing alloys may be implanted in patients as joint prostheses, plates and screws for fractured bones, surgical clips and steel sutures (Grandjean, 1984). Corrosion of these prostheses and implants can result in accumulation of alloy-specific metals in the surrounding soft tissues and in release of nickel to the extracellular fluid (Sunderman *et al.*, 1986a, 1989a).

High concentrations of nickel have been reported in human albumin solutions prepared by six manufacturers for intravenous infusion. In three lots that contained 50 g/l albumin, the average nickel concentration was 33 µg/l (range, 11-17 µg/l); in nine lots that contained 250 g/l albumin, the average nickel concentration was 83 µg/l (range, 26-222 µg/l) (Leach & Sunderman, 1985). Meglumine diatrizoate ('Renografin-76'), an X-ray contrast medium, tends to be contaminated with nickel. Seven lots of this preparation (containing 760 g/l diatrizoate) contained

Table 19. Nickel concentrations in dialysis fluids and in serum specimens from patients with chronic renal disease (CRD)[a]

Region and patients	No. of subjects	Ni conc. in dialysis fluid (μg/l)	Serum Ni concentration (μg/l)	
			Pre-dialysis	Post-dialysis
USA				
Healthy controls	30		0.3 ± 0.2	
Non-dialysed CRD patients	7		0.6 ± 0.3	
CRD patients on haemodialysis				
Hospital A	40	0.82	6.2 ± 1.8	7.2 ± 2.2
Hospital B	9	0.40-0.42	3.9 ± 2.0	5.2 ± 2.5
Hospital C	10	0.68	3.0 ± 1.3	3.7 ± 1.3
USA				
Healthy controls	50		0.4 ± 0.2	
CRD patients on haemodialysis	28		3.7 ± 1.5	
UK and Hong Kong				
Healthy controls	71		1.0 (< 0.6-3.0)	
Non-dialysed CRD patients	31		1.6 (< 0.6-3.6)	
CRD patients on haemodialysis				
Hospital A	25	2-3	8.6 (0.6-16.6)	8.8 (3.0-21.4)
Hospital B	16		2.9 (1.8-4.0)	3.4 (2.2-5.4)
CRD patients on peritoneal dialysis	13	2-3	8.6 (5.4-11.4)	

[a]From Sunderman *et al.* (1986a)

nickel at 144 ± 44 μg/l. Serum nickel concentrations in 11 patients who received intra-arterial injections of 'Renografin-76' (164 ± 10 ml per patient [giving 19.1 ± 4.0 μg Ni per patient]) for coronary arteriography increased from a pre-injection level of 1.33 μg/l (range, 0.11-5.53 μg/l) to 2.95 μg/l (range, 1.5-7.19 μg/l) 15 min post-injection. Serum levels remained significantly elevated for 4 h and returned to baseline levels only 24 h post-injection (Leach & Sunderman, 1987).

(j) *Regulatory status and guidelines*

Occupational exposure limits for nickel in various forms are given in Table 20.

Table 20. Occupational exposure limits for airborne nickel in various forms[a]

Country or region	Year	Nickel species	Concentration (mg/m^3)	Interpretation[b]
Belgium	1987	Nickel metal and insoluble nickel compounds (as Ni)	0.1	TWA
		Nickel carbonyl (as Ni)	0.35	TWA
Brazil	1987	Nickel carbonyl (as Ni)	0.28	TWA
Chile	1987	Soluble nickel compounds (as Ni)	0.08	TWA
China	1987	Nickel carbonyl (as Ni)	0.001	TWA
Denmark	1988	Nickel metal	0.5	TWA
		Nickel carbonyl	0.007	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
		Insoluble nickel compounds (as Ni)	1	TWA
Finland	1987	Nickel metal	1	TWA
		Nickel carbonyl	0.007	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
France	1986	Nickel sulfide (as Ni)	1	TWA
		Nickel compounds (as Ni)	0.25	TWA
German Democratic Republic	1987	Nickel carbonyl (as Ni)	0.01	TWA
		Nickel compounds (as Ni)	0.5	STEL
		Nickel carbonyl (as Ni)	0.03	STEL
Hungary	1987	Nickel compounds (as Ni)	0.005	TWA/STEL
		Nickel carbonyl (as Ni)	0.007	TWA/STEL
India	1987	Nickel carbonyl (as Ni)	0.35	TWA
Indonesia	1987	Nickel metal and insoluble nickel compounds (as Ni)	1	TWA
		Nickel carbonyl (as Ni)	0.007	TWA
Italy	1987	Nickel carbonyl (as Ni)	0.007	TWA
Japan	1987	Nickel	1	TWA
		Nickel carbonyl (as Ni)	0.007	TWA
Mexico	1987	Nickel metal and insoluble nickel compounds (as Ni)	1	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
		Nickel carbonyl (as Ni)	0.35	TWA

Table 20 (contd)

Country or region	Year	Nickel species	Concentration (mg/m^3)	Interpretation[b]
Netherlands	1986	Nickel	1	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
		Nickel carbonyl (as Ni)	0.35	TWA
Poland	1987	Nickel carbonyl (as Ni)	0.007	TWA
Romania	1987	Nickel carbonyl (as Ni)	0.002	TWA
		Nickel carbonyl (as Ni)	0.005	Ceiling
Sweden	1987	Nickel metal	0.5	TWA
		Nickel carbonyl	0.007	TWA
		Nickel subsulfide	0.01	TWA
		Other nickel compounds (as Ni)	0.1	TWA
Switzerland	1987	Nickel metal and insoluble nickel compounds (as Ni)	0.5	TWA
		Soluble nickel compounds (as Ni)	0.05	TWA
Taiwan	1987	Nickel carbonyl (as Ni)	0.35	TWA
UK	1987	Nickel and insoluble nickel compounds (as Ni)	1	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA
		Soluble nickel compounds (as Ni)	0.3	STEL (10 min)
		Insoluble nickel compounds (as Ni)	3	STEL (10 min)
		Nickel carbonyl (as Ni)	0.35	TWA
USA				
ACGIH	1988	Nickel metal; nickel sulfide roasting, fume and dust (as Ni)	1	TWA
		Soluble compounds (as Ni)	0.1	TWA
		Nickel carbonyl	0.35	TWA
NIOSH	1988	Nickel, inorganic compounds (as Ni)	0.015	TWA
		Nickel carbonyl	0.007	TWA
OSHA	1987	Metallic nickel	1	TWA
		Nickel carbonyl	0.007	TWA
		Soluble nickel compounds (as Ni)	0.1	TWA

Table 20 (contd)

Country or region	Year	Nickel species	Concentration (mg/m^3)	Interpretation[b]
USSR	1987	Nickel metal and insoluble nickel compounds (as Ni)	0.5	MAC
		Nickel carbonyl (as Ni)	0.0005	MAC
		Nickel monoxide, oxide, sulfide	0.5	MAC

[a]From Arbeidsinspectie, 1986; Institut National de Recherche et de Sécurité, 1986; National Institute for Occupational Safety and Health (NIOSH), 1988; Arbetarskyddsstyrelsens, 1987; Cook, 1987; Health and Safety Executive, 1987; Työsuojeluhallitus, 1987; US Occupational Safety and Health Administration (OSHA), 1987; American Conference of Governmental Industrial Hygienists (ACGIH), 1988; Arbejdstilsynet, 1988

[b]TWA, time-weighted average; STEL, short-term exposure limit; MAC, maximum allowable concentration

2.4 Analysis

Typical methods for the analysis of nickel in air, water, food and biological materials are summarized in Table 21. A method has been developed for classifying nickel in airborne dust samples into four species — 'water-soluble', 'sulfidic', 'metallic' and 'oxidic' — on the basis of a sequential leaching procedure (Blakeley & Zatka, 1985; Zatka, 1987, 1988; Zatka *et al.*, undated).

Atomic absorption spectrometry and differential pulse anodic stripping voltammetry (DPASV) are the most common methods for analysis of nickel in environmental and biological media. Air samples are collected on cellulose ester membrane filters, wet digested with nitric acid—perchloric acid and analysed by electrothermal atomic absorption spectrometry (EAAS) or inductively coupled argon plasma emission spectrometry (ICP) (National Institute for Occupational Safety and Health, 1984; Kettrup *et al.*, 1985). The National Institute for Occupational Safety and Health (1977b, 1981) has recommended standard procedures for personal air sampling and analysis of nickel. The routine procedure does not permit identification of individual nickel compounds.

Assessment of individual nickel compounds, especially as components of complex mixtures, necessitates procedures such as X-ray diffraction and would not be feasible for routine monitoring. Sampling and analytical methods used to monitor air, water and soil have been summarized (US Environmental Protection Agency, 1986).

Nickel concentrations in blood, serum or urine are used as biological indicators of exposure to or body burden of nickel. Biological monitoring as a part of biomedical surveillance has been evaluated in several reviews (Aitio, 1984; Norseth,

Table 21. Methods for the analysis of nickel

Sample matrix	Sample preparation	Assay procedure[a]	Sensitivity/detection limit	Reference
Air	Collect on cellulose ester membrane filter; digest with nitric acid and perchloric acid	AAS	–	National Institute for Occupational Safety and Health (1981)
	Collect on cellulose acetate membrane filter; digest with nitric acid and hydrochloric acid	AAS	1 μg absolute; 10 μg/m³ (sample volume, 0.1 m³)	Hauptverband der gewerblichen Berufsgenossenschaften (1981)
	Collect on cellulose ester membrane filter; digest with nitric acid and perchloric acid	ICP	1.5 μg/sample	National Institute for Occupational Safety and Health (1984)
	Collect on cellulose ester membrane filter; digest with nitric acid	AAS	20 ng/m³ (sample volume, 1.5 m³)	Kettrup *et al.* (1985)
Water	Chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	AAS	0.04 μg/l	McNeely *et al.* (1972)
	Filter; irradiate with ultraviolet	DPASV (dimethylglyoxime-sensitized)	1 ng/l	Pihlar *et al.* (1981)
	Chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	EAAS	0.2 μg/l	Sunderman (1986b)
Food	Digest with acid	AAS	–	Evans *et al.* (1978)
	Wet digest with nitric acid, hydrogen peroxide and sulfuric acid	DPASV (dimethylglyoxime-sensitized)	1 ng/l digestion solution	Pihlar *et al.* (1981)
	Dry ash	DPASV (dimethylglyoxime-sensitized)	5 ng/sample	Meyer & Neeb (1985)
	Dry ash, chelate with sodium(ditrifluorethyl)dithiocarbamate	Chelate-GC	100 ng/sample	Meyer & Neeb (1985)
Blood	Wet digest with nitric acid, hydrogen peroxide and sulfuric acid	DPASV (dimethylglyoxime-sensitized)	1 ng/l digestion solution	Pihlar *et al.* (1981)

Table 21 (contd)

Sample matrix	Sample preparation	Assay procedure[a]	Sensitivity/detection limit	Reference
Serum/whole blood	Digest with nitric acid; heat	EAAS (Zeeman)	0.05 µg/l serum 0.1 µg/l whole blood	Sunderman *et al.* (1984a)
Body fluids/ tissues	Digest with nitric acid, perchloric acid and sulfuric acid; chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	EAAS	0.2 µg/l body fluids 0.4 µg/kg tissues	Sunderman (1986b)
Tissues	Homogenize; digest with nitric acid, perchloric acid and sulfuric acid	EAAS (Zeeman)	0.01 µg/g dry wt	Sunderman *et al.* (1985a)
	Digest with nitric acid and sulfuric acid	EAAS (Zeeman)	0.8 µg/g wet wt	Raithel *et al.* (1987)
Serum/urine	Digest with nitric acid, perchloric acid and sulfuric acid; chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	EAAS	–	Brown *et al.* (1981)
Urine	Chelate; extract with ammonium pyrrolidine dithiocarbamate: methyl isobutyl ketone	EAAS	0.5 µg/l	Schaller & Zober (1982)
	Digest with nitric acid, perchloric acid and sulfuric acid	DPASV	1 µg/l	Schramel *et al.* (1985)
	Chelate; extract with hexamethylene ammonium: hexamethylene dithiocarbamate: diisopropylketone	AAS	0.2 µg/l	Angerer & Schaller (1985)
	Dilute with nitric acid	EAAS (Zeeman)	0.5 µg/l	Sunderman *et al.* (1986b)
	Dilute directly with nitric acid	EAAS	1.2 µg/l	Kiilunen *et al.* (1987)

[a]AAS, flameless atomic absorption spectrometry; ICP, inductively coupled argon plasma spectrometry; DPASV, differential pulse anodic stripping voltammetry; EAAS, electrothermal atomic absorption spectrometry; GC, gas chromatography

1984; Sunderman *et al.*, 1986a). Choice of specimen, sampling strategies, specimen collection, transport, storage and contamination control are of fundamental importance for an adequate monitoring programme (Sunderman *et al.*, 1986a). As discussed in recent reviews (Stoeppler, 1980; Schaller *et al.*, 1982; Stoeppler, 1984a,b; Sunderman *et al.*, 1986a, 1988a), EAAS and DPASV are practical, reliable techniques that furnish the requisite sensitivity for measurements of nickel concentrations in biological samples. The detection limits for determination of nickel by EAAS with Zeeman background correction are approximately 0.45 µg/l for urine, 0.1 µg/l for whole blood, 0.05 µg/l for serum or plasma, and 10 ng/g (dry wet) for tissues, foods and faeces (Andersen *et al.*, 1986; Sunderman *et al.*, 1986a,b; Kiilunen *et al.*, 1987; Angerer & Heinrich-Ramm, 1988). An EAAS procedure for the determination of nickel in serum and urine, which was developed on the basis of collaborative interlaboratory trials involving clinical biochemists in 13 countries, has been accepted as a reference method by the International Union of Pure and Applied Chemists (Brown *et al.*, 1981). This procedure, with additional applications for analysis of nickel in biological matrices, water and intravenous fluids, has also been accepted as a reference method by the IARC (Sunderman, 1986b). A new working method based on EAAS and Zeeman background correction for the analysis of nickel in serum, whole blood, tissues, urine and faeces has been recommended (Sunderman *et al.*, 1986a,b, 1988a). Sample preparation depends on the specimen and involves acid digestion for tissue and faeces, protein precipitation with nitric acid and heat for serum and whole blood, and simple acidification for urine.

Greater sensitivity can be achieved with DPASV analysis using a dimethylglyoxime-sensitized mercury electrode; this method has been reported to have a detection limit of 1 ng/l for determination of nickel in biological media (Flora & Nieboer, 1980; Pihlar *et al.*, 1981; Ostapczuk *et al.*, 1983). However, DPASV techniques are generally more cumbersome and time consuming than EAAS procedures. Isotope dilution mass spectrometry provides the requisite sensitivity, specificity and precision for determination of nickel (Fassett *et al.*, 1985) but has not yet been used to analyse nickel in biological samples.

Nickel carbonyl has been measured in air and exhaled breath by gas chromatography and chemiluminescence (Sunderman *et al.*, 1968; Stedman *et al.*, 1979).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals[1]

Experimental studies on animals exposed to nickel and various nickel compounds were reviewed previously in the *IARC Monographs* (IARC, 1976, 1987). Recent reviews on the biological and carcinogenic properties of nickel have been compiled by Fairhurst and Illing (1987), Kasprzak (1987) and Sunderman (1989), among others. In addition, a detailed document on the health effects of nickel has been prepared for the Ontario (Canada) Ministry of Labour (Odense University, 1986). A comprehensive technical report on nickel, emphasizing mutagenicity and carcinogenicity, was published by the European Chemical Industry Ecology and Toxicology Centre (1989).

(*a*) *Metallic nickel and nickel alloys*

(i) *Inhalation*

Mouse: A group of 20 female C57Bl mice, two months of age, was exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure; particle diameter, $\leq$4 μm) for 6 h per day on four or five days per week for 21 months. All mice had died by the end of the experiment. No lung tumour was observed. No control group was available (Hueper, 1958). [The Working Group noted the short duration of treatment.]

Rat: Groups of 50 male and 50 female Wistar rats and 60 female Bethesda black rats, two to three months of age, were exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure nickel; particle diameter, $\leq$4 μm) for 6 h per day on four or five days per week for 21 months and observed up to 84 weeks. Histological examination of the lungs of 50 rats showed numerous multicentric, adenomatoid alveolar lesions and bronchial proliferations that were considered by the author as benign neoplasms. No specific control was included in the study (Hueper, 1958).

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[1]The Working Group was aware of studies in progress of the carcinogenicity of nickel, nickel acetate tetrahydrate, nickel alloys, nickel–aluminium alloys, nickel chloride hexahydrate, nickel oxide, nickel sulfide and nickel sulfate hexa- and heptahydrate in experimental animals by intraperitoneal, subcutaneous, inhalation and intratracheal administration (IARC, 1988b).

In a further experiment with Bethesda black rats, exposure to metallic nickel powder (99.95% nickel; particle diameter, 1-3 μm) was combined with 20-35 ppm (50-90 mg/m^3) sulfur dioxide as a mucosal irritant; powdered chalk was added to prevent clumping. Exposure was for 5-6 h per day [nickel concentration unspecified]. Forty-six of 120 rats lived for longer than 18 months. No lung tumour was observed, but many rats developed squamous metaplasia and peribronchial adenomatoses (Hueper & Payne, 1962).

Guinea-pig: A group of 32 male and 10 female strain 13 guinea-pigs, about three months of age, was exposed by inhalation to 15 mg/m^3 metallic nickel powder (> 99% pure nickel) for 6 h per day on four or five days per week for 21 months. Mortality was high: only 23 animals survived to 12 months and all animals had died by 21 months. Almost all animals developed adenomatoid alveolar lesions and terminal bronchiolar proliferations. No such lesion was observed in nine controls. One treated guinea-pig had an anaplastic intra-alveolar carcinoma, and another had an apparent adenocarcinoma metastasis in an adrenal node, although the primary tumour was not identified (Hueper, 1958).

(ii) *Intratracheal instillation*

Rat: Two groups of female Wistar rats [number unspecified], 11 weeks of age, received either ten weekly intratracheal instillations of 0.9 mg metallic nickel powder [purity unspecified] or 20 weekly injections of 0.3 mg metallic nickel powder in 0.3 ml saline (total doses, 9 and 6 mg, respectively) and were observed for almost 2.5 years. Lung tumour incidence in the two groups was 8/32 (seven carcinomas, one mixed) and 10/39 (nine carcinomas, one adenoma), respectively; no lung tumour developed in 40 saline-treated controls maintained for up to 124 weeks. Pathological classification of the tumours in the two groups combined revealed one adenoma, four adenocarcinomas, 12 squamous-cell carcinomas and one mixed tumour. Average time to observation of the tumours was 120 weeks, the first tumour being observed after 98 weeks (Pott *et al.*, 1987).

Hamster: In a study reported in an abstract, groups of 100 Syrian golden hamsters received either a single intratracheal instillation of 10, 20 or 40 mg of metallic nickel powder (particle diameter, 3-8 μm) or of one of two nickel alloy powders (particle diameter, 0.5-2.5 μm; alloy I: 26.8% nickel, 16.2% chromium, 39.2% iron, 0.04% cobalt; alloy II: 66.5% nickel, 12.8% chromium, 6.5% iron, 0.2% cobalt) or four intratracheal instillations of 20 mg of one of the substances every six months (total dose, 80 mg). In the groups receiving single instillations of alloy II, the incidence of malignant intrathoracic tumours was reported as 1, 8 and 12%, respectively, suggesting a dose-response relationship. In the group receiving multiple instillations of alloy II, 10% of the animals developed intrathoracic malignant neoplasms, diagnosed as fibrosarcomas, mesotheliomas and rhabdomyosarcomas. Metallic

nickel induced comparable numbers and types of intrathoracic neoplasms, but no tumour was observed in animals treated with alloy I or in control animals (Ivankovic *et al.*, 1987).

A group of approximately 60 male and female Syrian golden hamsters (strain Cpb-ShGa 51), ten to 12 weeks of age, received 12 intratracheal instillations of 0.8 mg metallic nickel powder (99.9% nickel; mass median diameter, 3.1 μm) in 0.15 ml saline at two-week intervals (total dose, 9.6 mg). Additional groups were treated similarly with 12 intratracheal instillations of 3 mg pentlandite (containing 34.3% nickel; total dose, 36 mg), 3 or 9 mg chromium/nickel stainless-steel dust (containing 6.79% nickel; total doses, 36 and 108 mg) or 9 mg chromium stainless-steel dust (containing 0.5% nickel; total dose, 108 mg). The median lifespan was 90-130 weeks in the different groups. Two lung tumours were observed: an adenocarcinoma in the group that received nickel powder and an adenoma in the pentlandite-treated group. No lung tumour was observed in vehicle-treated controls or in the groups treated with stainless-steels (Muhle *et al.*, 1990). [The Working Group noted that no lung tumour was observed in the positive control group.]

(iii) *Intrapleural administration*

Rat: A group of 25 female Osborne-Mendel rats, six months of age, received injections of a 12.5% suspension of metallic nickel powder in 0.05 ml lanolin into the right pleural cavity [6.25 mg nickel powder] once a month for five months. A group of 70 rats received injections of lanolin only. The experiment was terminated after 16 months. Four of the 12 treated rats that were examined had developed round-cell and spindle-cell sarcomas at the site of injection; no control animal developed a local tumour [$p < 0.01$] (Hueper, 1952).

A group of five male and five female Fischer 344 rats, 14 weeks of age, received injections of 5 mg metallic nickel powder suspended in 0.2 ml saline into the pleura (total dose, 25 mg) once a month for five months. Two rats developed mesotheliomas within slightly over 100 days; no tumour occurred in 20 controls (Furst *et al.*, 1973). [The Working Group noted the limited reporting of the experiment.]

(iv) *Subcutaneous administration*

Rat: Groups of five male and five female Wistar rats, four to six weeks of age, received four subcutaneous implants of pellets (approximately 2×2 mm) of metallic nickel or nickel-gallium alloy (60% nickel) used for dental prostheses and were observed for 27 months. Local sarcomas were noted in 5/10 rats that received the metallic nickel and in 9/10 rats that received the nickel-gallium alloy. No local tumour occurred in ten groups of rats that received similar implants of other dental materials (Mitchell *et al.*, 1960).

(v) *Intramuscular administration*

Rat: A group of ten female hooded rats, two to three months of age, received a single intramuscular injection of 28.3 mg pure metallic nickel powder in 0.4 ml fowl serum into the right thigh. All animals developed rhabdomyosarcomas at the injection site within 41 weeks. Historical controls injected with fowl serum alone did not develop local tumours (Heath & Daniel, 1964).

Groups of 25 male and 25 female Fischer 344 rats [age unspecified] received five monthly intramuscular injections of 5 mg metallic nickel powder in 0.2 ml trioctanoin. Fibrosarcomas occurred in 38 treated animals but in none of a group of 25 male and 25 female controls given trioctanoin alone (Furst & Schlauder, 1971).

Two groups of ten male Fischer 344 rats, three months of age, received a single intramuscular injection of metallic nickel powder (3.6 or 14.4 mg/rat) in 0.5 ml penicillin G procaine. Surviving rats were killed 24 months after the injection. Sarcomas at the injection site were found in 0/10 and 2/9 treated rats, respectively, as compared with 0/20 vehicle controls (Sunderman & Maenza, 1976). [The Working Group noted the small number of animals used.]

Groups of 20 WAG rats [sex and age unspecified] received a single intramuscular injection of 20 mg metallic nickel powder in an oil vehicle [type unspecified]. A group of 56 control rats received 0.3 ml of the vehicle alone. Local sarcomas developed in 17/20 treated and 0/56 control rats (Berry *et al.*, 1984). [The Working Group noted the inadequate reporting of tumour induction.]

Groups of 20 or 16 male Fischer 344 rats, two to three months of age, received a single intramuscular injection of 14 mg metallic nickel powder (99.5% pure) or 14 mg (as nickel) of a ferronickel alloy ($NiFe_{1-6}$) in 0.3-0.5 ml penicillin G vehicle into the right thigh. Of the 20 rats receiving nickel powder, 13 developed tumours at the site of injection (mainly rhabdomyosarcomas), with an average latency of 34 weeks. No local tumour developed in the 16 rats given the ferronickel alloy, in 44 controls given penicillin G or in 40 controls given glycerol (Sunderman, 1984).

Groups of 40 male inbred WAG rats, 10-15 weeks of age, received a single intramuscular injection of 20 mg metallic nickel in paraffin oil. One group also received intramuscular injections of interferon at 5×10^4 U/rat twice a week beginning in the tenth week after nickel treatment. Rhabdomyosarcomas occurred in 14/30 and 5/10 rats in the two groups, respectively. Metallic nickel depressed natural killer cell activity. Prospective analysis of individual natural killer cell responses indicated that a persistent depression was restricted to rats that subsequently developed a tumour (Judde *et al.*, 1987).

Hamster: Furst and Schlauder (1971) compared the tumour response in Syrian hamsters with that of Fischer 344 rats (see above) to metallic nickel powder. Groups of 25 male and 25 female hamsters, three to four weeks old, received five

monthly intramuscular injections of 5 mg nickel powder in 0.2 ml trioctanoin. Two fibrosarcomas occurred in males. No local tumour occurred in 25 male and 25 female controls injected with trioctanoin alone.

(vi) *Intraperitoneal administration*

Rat: As reported in an abstract, a group of male and female Fischer rats [numbers unspecified], weighing 80-100 g, received intraperitoneal injections of 5 mg metallic nickel powder in 0.3 ml corn oil twice a month for eight months. A control group received injections of corn oil only. In the treated group, 30-50% of rats were reported to have developed intraperitoneal tumours (Furst & Cassetta, 1973).

A group of 50 female Wistar rats, 12 weeks of age, received ten weekly intraperitoneal injections of 7.5 mg metallic nickel powder [purity unspecified] (total dose, 75 mg). Abdominal tumours (sarcomas, mesotheliomas or carcinomas) developed in 46/48 (95.8%) rats at an average tumour latency of approximately eight months. Concurrent controls were not reported, but, in non-concurrent groups of saline controls, abdominal tumours were found in 0-6% of animals (Pott *et al.*, 1987).

Groups of female Wistar rats, 18 weeks of age, received single or repeated intraperitoneal injections of metallic nickel powder (100% nickel) or of one of three nickel alloys in 1 ml saline once or twice a week. All animals were sacrificed 30 months after the first injection. The incidences of local sarcomas and mesotheliomas in the peritoneal cavity are shown in Table 22. A dose-response trend was apparent for metallic nickel, and the tumour responses to the nickel alloys increased with the proportion of nickel present and the dose (Pott *et al.*, 1989, 1990). [The Working Group noted that the results at 30 months were available as an extended abstract only.]

(vii) *Intravenous administration*

Mouse: A group of 25 male C57Bl mice, six weeks old, received two intravenous injections of 0.05 ml of a 0.005% suspension of metallic nickel powder in 2.5% gelatin into the tail vein. Nineteen animals survived more than 52 weeks, and six survived over 60 weeks. No tumour was observed. No control group was used (Hueper, 1955). [The Working Group noted the short period of observation.]

Rat: A group of 25 Wistar rats [sex unspecified], 24 weeks of age, received intravenous injections of 0.5 ml/kg bw metallic nickel powder as a 0.5% suspension in saline into the saphenous vein once a week for six weeks. Seven rats developed sarcomas in the groin region along the injection route [probably from seepage at the time of treatment]. No control group was used (Hueper, 1955).

Table 22. Tumour responses of rats to intraperitoneal injection of nickel and nickel alloys[a]

Compound	Total dose (mg, as Ni)	Schedule	Mesotheliomas at two years	Sarcomas at two years	Local tumours at 30 months[b]
Metallic nickel	6	Single injection	3	0	4/34
	12	2 × 6 mg	3	2	5/34
	25	25 × 1 mg	16	9	25/35
Alloy (50% Ni)	50	Single injection	1	7	8/35
	150	3 × 50 mg	2	8	13/35
Alloy (29% Ni)[c]	50	Single injection	0	0	2/33
	100	2 × 50 mg	0	1	1/36
Alloy (66% Ni)[d]	50	Single injection	0	11	12/35
	150	3 × 50 mg	4	20	22/33
Saline		3 × 1 ml	0	1	1/33
		50 × 1 ml	0	0	0/34

[a]From Pott *et al.* (1989, 1990)
[b]Results not given separately for mesotheliomas and sarcomas
[c]Before milling: 32% Ni, 21% Cr, 0.8% Mn, 55% Fe
[d]Before milling: 74% Ni, 16% Cr, 7% Fe

(viii) *Intrarenal administration*

Rat: A group of 20 female Sprague-Dawley rats, weighing 120-140 g, received an injection of 5 mg metallic nickel in 0.05 ml glycerine into each pole of the right kidney. No renal carcinoma or erythrogenic response developed within the 12-month period of observation (Jasmin & Riopelle, 1976).

Groups of male Fischer 344 rats, approximately two months of age, received an intrarenal injection of 7 mg metallic nickel powder or of a ferronickel alloy ($NiFe_{1\cdot6}$; 7 mg Ni per rat) in 0.1 or 0.2 ml saline solution into each pole of the right kidney. The study was terminated after two years; the median survival time was 100 weeks in the two treated groups compared with 91 weeks in controls. Renal cancers occurred in 0/18 and 1/14 rats, respectively, compared with 0/46 saline-treated controls. The tumour was a nephroblastoma which was observed at 25 weeks (Sunderman *et al.*, 1984b).

(ix) *Implantation of ear-tags*

Rat: In a study carried out to assess the carcinogenicity of cadmium chloride, 168 male Wistar rats, six weeks of age, received identification ear-tags fabricated of nickel-copper alloy (65% Ni, 32% Cu, 1% Fe, 1% Mn). A total of 14 tumours, mostly osteosarcomas, developed within 104 weeks at the site of implantation. The authors

implicated nickel in the alloy as the probably causative agent and apparent local microbial infection as a contributory factor (Waalkes *et al.*, 1987).

(x) *Other routes of administration*

Rat: In groups of 20 WAG rats [sex and age unspecified] *subperiosteal injection* of 20 mg metallic nickel powder resulted in local tumours in 11/20 rats; *intramedullary injection* of 20 mg metallic nickel resulted in local tumours in 9/20 rats (Berry *et al.*, 1984). [The Working Group noted the absence of controls and the inadequate reporting of tumour induction.]

(xi) *Administration with known carcinogens*

Rat: Four groups of female Wistar rats [initial numbers unspecified], four to six weeks old, received intratracheal instillations of 1 or 5 mg 20-methylcholanthrene (MC) alone or with 10 mg metallic nickel powder (99.5% nickel). A fifth group received 10 mg metallic nickel powder only. At 12 weeks, squamous-cell carcinomas had developed as follows: 5 mg MC, 2/7; 5 mg MC plus Ni, 3/5; 1 mg MC, 0/8; 1 mg MC plus Ni, 0/7; metallic Ni alone, 0/7. Pretumorous lesions were more marked and the amount of epithelial metaplasia enhanced in groups receiving the combined treatment or MC only (Mukubo, 1978). [The Working Group noted the small number of animals used and the short duration of observation.]

(*b*) *Nickel oxides and hydroxides*

The compounds considered under this heading include a variety of substances of nominally similar composition, which, however, may vary considerably due to differences in production methods. These differences were not generally defined in the studies described below, beyond the relatively recent designation of green and black nickel oxide.

(i) *Inhalation*

Rat: Groups of six or eight male Wistar rats, two months of age, were exposed by inhalation to 0.6 or 8.0 mg/m^3 nickel monoxide (green) particles (median aerodynamic diameter, 1.2 μm) for 6 h per day on five days per week for one month, after which they were maintained with no further exposure for an additional 20 months. Histopathological examination revealed one adenocarcinoma and one adenomatous lesion of the lung in the low-exposure rats and one adenomatosis in the high-exposure group. Bronchial glandular hyperplasia was seen in five and six rats in the low- and high-dose groups, respectively; a malignant histiocytoma that emanated from the paranasal region was noted in the upper respiratory tract of one rat [group unspecified]. None of the five control rats developed these lesions, although both control and exposed animals exhibited some squamous metaplasia (Horie *et al.*, 1985). [The Working Group noted the small number of animals used and the short exposure period.]

Groups of 40 and 20 male Wistar rats, five weeks of age, were exposed by inhalation to 60 and 200 μg/m³ nickel as nickel monoxide aerosol (particle size, <0.3 μm) continuously for 18 months, followed by an observation period of one year under normal atmospheric conditions. At 24 months, 80% of animals in the treatment group had died, and at termination of the study (30 months) 62.5% of controls had died. No carcinogenic effect was observed (Glaser *et al.*, 1986). [The Working Group noted that the toxic effects, particularly alveolar proteinosis, were severe, that the survival of the animals was too short for carcinogenicity to be evaluated fully, and that nickel oxide aerosols were generated by atomization of aqueous nickel acetate solutions.]

Hamster: A group of 51 male Syrian golden hamsters, two months of age, was exposed by inhalation to a mean aerosol concentration of 53.2 mg/m³ nickel monoxide (mean particle diameter, 0.3 μm) for 7 h per day on five days per week for life. Another group of 51 males was exposed to nickel monoxide plus cigarette smoke. Two control groups of 51 animals were exposed to smoke and sham dust or to sham smoke and sham dust. Massive pneumoconiosis with lung consolidation developed in the nickel monoxide-exposed animals but did not affect their lifespan. Mean lifespan was 19.6 ± 1.6 months for animals exposed to smoke and nickel monoxide, 16.1 ± 1.1 for sham-exposed nickel oxide-treated animals and 19.6 ± 1.4 and 15.3 ± 1.3 months for the respective controls. No significant increase in the incidence of respiratory tumours or any evidence of cocarcinogenic interaction with cigarette smoke was noted for nickel monoxide. One osteosarcoma occurred in the nickel monoxide-treated group and one osteosarcoma and one rhabdomyosarcoma in the muscle of the thorax were seen in the group given nickel monoxide plus cigarette smoke (Wehner *et al.*, 1975, 1979).

(ii) *Intratracheal instillation*

Rat: Groups of female Wistar rats [numbers unspecified], 11 weeks of age, received ten weekly intratracheal instillations of 5 or 15 mg nickel as nickel monoxide (99.99% pure) in 0.3 ml saline to give total doses of 50 and 150 mg nickel, respectively. A control group of 40 rats received injections of saline only and were observed for 124 weeks. Lung tumour incidence in the two treated groups was 10/37 (27%) and 12/38 (31.6%), respectively; the tumours in the two groups consisted of four adenocarcinomas, two mixed tumours and 16 squamous-cell carcinomas. No lung tumour occurred in controls (Pott *et al.*, 1987).

Hamster: In an experiment designed to study the effects of particulates on the carcinogenesis of *N*-nitrosodiethylamine, groups of 25 male and 25 female hamsters [strain unspecified], five weeks old, received intratracheal instillations of 0.2 ml of a suspension of 2 g nickel monoxide (particle size, 0.5-1.0 μm) in 100 ml 0.5% w/v gelatin/saline once a week for 30 weeks. A group of 50 controls received injections

of carbon dust in the vehicle. Only three hamsters in each group survived beyond 48 weeks. One respiratory tract tumour [unspecified] was found in the 47 nickel monoxide-treated animals that were necropsied and four in controls. A high incidence of respiratory-tract tumours was observed in animals treated with *N*-nitrosodiethylamine alone (Farrell & Davis, 1974). [The Working Group noted the poor survival of treated and control animals.]

(iii) *Intrapleural administration*

Rat: A group of 32 male Wistar rats, three months of age, received a single intrapleural injection of 10 mg nickel monoxide in 0.4 ml saline suspension. A positive control group of 32 rats received a 10 mg injection of crocidolite, and a negative control group of 32 rats received saline alone. After 30 months, 31/32 rats in the nickel monoxide-treated group had developed injection-site tumours (mostly rhabdomyosarcomas). Median survival time was 224 days. Nine of 32 rats in the crocidolite-treated group had local tumours, but none of the saline controls developed local sarcomas (Skaug *et al.*, 1985).

(iv) *Intramuscular administration*

Mouse: Two groups of 50 Swiss and 52 C3H mice, equally divided by sex, two to three months of age, received single intramuscular injections of 5 mg nickel monoxide in penicillin G procaine into each thigh muscle and were observed for up to 476 days. Local sarcomas (mainly fibrosarcomas) occurred in 33 Swiss and 23 C3H mice. No control was reported (Gilman, 1962).

Rat: A group of 32 Wistar rats [sex unspecified], two to three months of age, received single intramuscular injections of 20 mg nickel monoxide powder into each thigh muscle and were observed for up to 595 days. Twenty-one rats developed a total of 26 tumours at the site of injection; 80% of the tumours were rhabdomyosarcomas, and the average latent period was 302 days. No control was reported (Gilman, 1962).

Groups of 20 Fischer rats [sex and age unspecified] received single intramuscular injections at two sites of either nickel hydroxide or nickel monoxide [dose unspecified] in aqueous penicillin G procaine. Local sarcomas developed in 15/20 (19 tumours at 40 sites) and 2/20 rats, respectively. Concurrent vehicle controls were not used. Seventeen of 20 animals given nickel subsulfide [dose unspecified] as positive controls developed local sarcomas. No tumour developed at the injection sites in two other groups of rats in the same experimental series injected intramuscularly with either nickel sulfate or nickel sulfide [presumed to be amorphous] (Gilman, 1966).

Ten male and ten female Wistar rats, weighing 150-170 g, received an intramuscular injection of 3 mg nickel trioxide powder. No control group was reported. No neoplasm developed at the injection site (Sosiński, 1975).

A group of 15 male Fischer 344 rats, two months of age, received a single intramuscular injection of nickel at 14 mg/rat as nickel monoxide (bunsenite, green-grey (Sunderman, 1984); 99.9% pure; particle diameter, <2 μm) in 0.3 ml of a 1:1 v/v glycerol:water vehicle into the right thigh and were observed for 104 weeks. Fourteen animals developed local sarcomas (mostly rhabdomyosarcomas) with a median tumour latency of 49 weeks and a median survival time of 58 weeks; metastases occurred in 4/14 rats. None of 40 control rats injected with vehicle alone developed tumours at the site of injection; 25/40 control rats were still alive at termination of the experiment (Sunderman & McCully, 1983).

Groups of 20 male Wistar rats, weighing 200-220 g, received a single intramuscular injection of 120 μmol [7.1 mg] nickel as one of three nickel hydroxide preparations — an air-dried gel, crystalline industrial nickel hydroxide and a freshly prepared colloidal nickel hydroxide — in 0.1 ml distilled water. A positive control group was treated with 120 μmol [7.1 mg] nickel as nickel subsulfide (see also p. 337) and a negative control group was treated with sodium sulfate. Seven rats treated with the colloidal preparation and one treated with the gel died from haematuria one to two weeks after the treatment. Six ulcerating, tumour-like growths developed between five and six months after treatment in the crystalline-treated group, but these regressed and were not included in tabulations. Local tumours occurred in 5/19 rats (four rhabdomyosarcomas, one fibrosarcoma) given the dried gel, 3/20 (all rhabdomyosarcomas) given the crystalline compound, 0/13 given the colloidal preparation, 16/20 positive controls and 0/20 negative controls (Kasprzak *et al.*, 1983). [See also pp. 360-361.]

In the study by Berry *et al.* (1984) described on p. 321, no tumour was induced by 20 mg nickel monoxide by either the intramuscular or subperiosteal route in groups of 20 rats.

In the study by Judde *et al.* (1987) described on p. 321, no tumour was induced by 20 mg nickel trioxide in ten rats.

(v) *Intraperitoneal administration*

Rat: A group of 50 female Wistar rats, 12 weeks of age, received two intraperitoneal injections of 500 mg nickel as nickel monoxide (99.99% pure); 46/47 of the animals developed abdominal tumours (sarcomas, mesotheliomas or carcinomas) with an average tumour latency of 31 months. Concurrent controls were not reported but, in other groups of saline controls, the incidence of abdominal tumours ranged from 0 to 6% (Pott *et al.*, 1987).

In a study described earlier (p. 322), single injections of 25 and 100 mg nickel as nickel monoxide induced local sarcomas and mesotheliomas in the peritoneal cavity in 12/34 and 15/36 female Wistar rats, respectively, after 30 months (Pott *et al.*,

1989, 1990). [The Working Group noted that the results at 30 months were available as an extended abstract only.]

(vi) *Intrarenal administration*

Rat: A group of 12 male Fischer 344 rats, two months of age, received an injection of nickel monoxide (green; 7 mg/rat nickel) in 0.1 or 0.2 ml saline into each pole of the right kidney and were observed for two years. No renal carcinoma was observed (Sunderman *et al.*, 1984b; see also p. 323).

(vii) *Intracerebral injection*

Rat: A group of ten male and ten female Wistar rats, weighing 150-170 g, received an intracerebral injection of 3 mg nickel trioxide powder into the cerebral cortex. No control group was reported. Cerebral sarcomas [gliomas] were observed in two rats that were killed at 14 and 21 months, respectively, and a meningioma was found in one rat that was killed at 21 months (Sosiński, 1975).

(*c*) *Nickel sulfides*

The experiments described below refer primarily to α-nickel subsulfide and to other crystalline forms of nickel sulfide, except where specifically stated that an amorphous form was tested.

(i) *Inhalation*

Rat: A group of 122 male and 104 female Fischer 344 rats [age unspecified] was exposed by inhalation to 0.97 mg/m^3 nickel subsulfide (particle diameter, < 1.5 μm) for 6 h per day on five days per week for 78 weeks. The remaining rats were observed for another 30 weeks, by which time survival was less than 5%. Survival of a group of 241 control rats exposed to filtered room air was 31% at 108 weeks. A significant increase in the incidence of benign and malignant lung tumours was observed compared to controls. Among treated rats, 14 malignant (ten adenocarcinomas, three squamous-cell carcinomas, one fibrosarcoma) and 15 benign lung tumour-bearing animals were identified; one adenocarcinoma and one adenoma developed among controls. The earliest tumour appeared at 76 weeks, and the average tumour latency was approximately two years. An elevated incidence of hyperplastic and metaplastic lung lesions was also noted among nickel subsulfide-treated rats (Ottolenghi *et al.*, 1974).

(ii) *Intratracheal instillation*

Mouse: Groups of 20 male B6C3F1 mice, eight weeks of age, received intratracheal instillations of 0.024, 0.056, 0.156, 0.412 or 1.1 mg/kg bw nickel subsulfide (particle size, < 2 μm) in saline once a week for four weeks and were observed for up to 27 months, at which time about 50% of the animals had died. Lung tumours

occurred in all groups; no significant difference from controls and no dose-response relationship was observed. No damage to the respiratory tract that was attributable to treatment was seen (Fisher *et al.*, 1986). [The Working Group noted the low doses used.]

Rat: Groups of 47, 45 and 40 female Wistar rats, 11 weeks of age, received intratracheal instillations of 0.063, 0.125 or 0.25 mg/animal nickel subsulfide in 0.3 ml saline (total doses, 0.94, 1.88 and 3.75 mg/animal) once a week for 15 weeks. At 120 weeks, 50% of the animals were still alive; the experiment was terminated at 132 weeks. The incidences of malignant lung tumours were 7/47, 13/45 and 12/40 in the low-, medium- and high-dose groups; 12 adenocarcinomas, 15 squamous-cell carcinomas and five mixed tumours occurred in the lungs of treated animals. No lung tumour occurred in 40 controls given 20 intratracheal injections of 0.3 ml saline (Pott *et al.*, 1987).

Hamster: In the study reported on p. 320 (Muhle *et al.*, 1990), no lung tumour was seen in 62 animals given 12 doses of 0.1 mg α-nickel subsulfide by intratracheal instillation. [The Working Group noted the low total dose given.]

(iii) *Intrapleural administration*

Rat: A group of 32 male Wistar rats, three months of age, received a single intrapleural injection of 10 mg nickel subsulfide in 0.4 ml saline. Average survival was 177 days. Local malignant tumours (mainly rhabdomyosarcomas) developed in 28/32 animals but in none of 32 saline-injected controls (Skaug *et al.*, 1985)

(iv) *Topical administration*

Hamster: Groups of male golden Syrian hamsters of the LVG/LAK strain, two to three months of age, were painted on the mucosa of the buccal pouches with 1 or 2 mg α-nickel subsulfide in 0.1 ml glycerol three times a week for 18 weeks (six to seven animals; total doses, 54 and 108 mg nickel subsulfide) or with 5 or 10 mg three times a week for 36 weeks (13-15 animals; total doses, 540 and 1080 mg nickel subsulfide), and were observed for more than 19 months. Two control groups received applications of glycerol. No tumour developed in the buccal pouch, oral cavity or intestinal tract in the treated or control groups. Squamous-cell carcinomas of the buccal pouch developed in all four hamsters that received applications of 1 mg dimethylbenz[*a*]anthracene in glycerol three times a week for 18 weeks (Sunderman, 1983b).

(v) *Intramuscular administration*

Mouse: Groups of 45 Swiss and 18 C3H mice, approximately equally divided by sex, two to three months of age, received single intramuscular injections of 5 mg nickel subsulfide into both or only one thigh muscle. Local tumours (mainly sarco-

mas) developed in 27 and nine mice, respectively. No control was reported (Gilman, 1962).

Three groups of ten female and one group of ten male NMRI mice, six weeks of age, received an injection of 10 mg labelled nickel subsulfide into the left thigh muscle, or of 5 mg into the interscapular subcutaneous tissue, in 0.1 ml olive oil:streptocillin (3:1). Two mice from each group were killed two months after injection for whole-body autoradiography; no tumour was seen at this stage. The remaining animals were autopsied at 14 months, when local sarcomas were seen in 7/8 and 4/8 females that received subcutaneous injections and in 4/8 males and 4/8 females that received intramuscular injections. Metastases to the lung, liver and regional lymph nodes occurred in approximately half of the 19 tumour-bearing mice. No control group was used (Oskarsson *et al.*, 1979).

Groups of four male and six female DBA/2 and five male and five female C57Bl6 mice, two to three months of age, received a single intramuscular injection of 2.5 mg α-nickel subsulfide in 0.1-0.5 ml penicillin G procaine solution into one thigh muscle. Local sarcomas developed in six DBA/2 ($p < 0.01$) and in five C57Bl6 ($p < 0.05$) mice, with median latent periods of 13 and 14 months, respectively. None of nine control mice of each strain injected with penicillin G alone developed a sarcoma (Sunderman, 1983b).

Rat: A group of 32 male and female Wistar rats, two to three months of age, received a single intramuscular injection of 20 mg nickel subsulfide into one or both thigh muscles. After an average of 21 weeks, 25/28 rats had developed 36 local tumours. Vehicle controls were not available, but two further groups of 30 rats each injected with ferrous sulfide did not develop tumours at the site of injection after 627 days (Gilman, 1962).

Groups of ten male and ten female Fischer rats, five months of age, were administered nickel subsulfide either by an intramuscular injection of 10 mg powder (particle size, 2-4 μm), by implantation of an intact 11-mm disc (500 mg), by implantation of 3-5-mm disc fragments or by implantation of 10 mg powder in a 0.45-μm porosity millipore diffusion chamber. Local tumours (mostly rhabdomysarcomas) developed in 71-95% of rats, which demonstrated diffusion of soluble nickel from the chambers. The mean tumour latency for the last group was 305 days, almost twice that for the other three groups. Among 19 controls given 38 implants of empty diffusion chambers, one tumour developed after 460 days. The authors considered that the experiment demonstrated that the induction of neoplasms by nickel subsulfide is a chemical rather than a physical (foreign-body) reaction and that phagocytosis is not essential for nickel tumorigenesis (Gilman & Herchen, 1963).

Groups of 15 Fischer rats received implants of nickel subsulfide discs (250 mg) or 8 × 1-mm discs of ferric oxide (control) in opposite sides of the gluteal

musculature. The nickel subsulfide discs were removed in a geometric sequence at two, four, eight... up to 256 days after implantation, and average tumour incidence after 256 days was 66%. The critical exposure (tissue contact) period necessary for nickel subsulfide to induce malignant transformation was 32-64 days (Herchen & Gilman, 1964).

Groups of 15 male and 15 female hooded and 15 male and 12 female NIH (Bethesda) black rats, two to three months of age, received injections of 10 mg nickel subsulfide in penicillin G procaine into each gastrocnemius muscle. NIH Black rats were less susceptible to local tumour induction (14/23 rats) than hooded rats (28/28). Massive phagocytic invasion of the nickel injection site occurred in the NIH black rats (Daniel, 1966).

Groups of 20 male and 20 female Fischer 344 rats, five weeks of age, received a single subcutaneous injection of 10 or 3.3 mg nickel subsulfide in 0.25 ml saline. Two further groups received single intramuscular injections of 10 or 3.3 mg nickel subsulfide. A group of 60 male and 60 female control rats received injections of 0.25 ml saline twice a week for 52 weeks, and a further control group received no treatment. At 18 months, the groups injected subcutaneously with nickel subsulfide had tumour incidences of 90 and 95%, and the groups injected intramuscularly had tumour incidences of 85% and 97%. Most tumours in both groups were rhabdomyosarcomas. No local tumour occurred in controls (Mason, 1972).

Groups of ten male Fischer 344 rats, three months of age, received intramuscular injections of amorphous nickel sulfide and α-nickel subsulfide in 0.5 ml penicillin G procaine suspension at two comparable dose levels (about 5 and 20 mg/rat), to provide 60 and 240 μg Ni per rat. A further group received injections of nickel ferrosulfide matte (85 and 340 μg atom of nickel per rat). Sarcomas at the injection site developed in 8/10 and 9/9 of the low- and high-dose nickel subsulfide-treated groups and in 1/10 and 8/10 of the low- and high-dose nickel ferrosulfide matte-treated groups, respectively. No local sarcoma developed in the groups given nickel sulfide, among control rats given penicillin G procaine suspension alone or in two control groups treated with metallic iron powder (Sunderman & Maenza, 1976).

Groups of 63 male and female inbred Fischer and 20 male and female hooded rats, ten to 14 weeks old, received an intramuscular injection of 10 mg nickel subsulfide in penicillin G procaine. Tumour-bearing rats were autopsied 30 days after detection of the tumour. Tumours occurred in 59/63 Fischer and 11/20 hooded rats; 81.9% of tumours in hooded rats metastasized, compared to 25.4% in Fischer rats. Metastatic lesions were observed in the heart, pleura, liver and adrenal glands, as well as in lungs and lymph nodes of nine hooded rats. Of the primary tumours, 67% were rhabdomyosarcomas (Yamashiro *et al.*, 1980).

Groups of 30 male Fischer 344 rats, approximately two months of age, received a single intramuscular injection of 0.6, 1.2, 2.5 or 5 mg nickel subsulfide. Local sarcomas were recorded in 7/30, 23/30, 28/30 and 29/30 of the animals, respectively [$p < 0.01$], indicating a dose-related increase in incidence. No such tumour developed in 60 untreated controls (Sunderman *et al.*, 1976). In an extension of this study, a total of 383 animals received injections of 0.63-20 mg α-nickel subsulfide. Sarcoma incidence at 62 weeks after treatment ranged from 24% at the lowest dose level to 100% at the highest dose level. Of the 336 sarcomas induced, 161 were rhabdomyosarcomas, 91 undifferentiated sarcomas, 72 fibrosarcomas, nine liposarcomas, two neurofibrosarcomas and one a haemangiosarcoma. Metastasis was seen in 137 of the 336 tumour-bearing animals (Sunderman, 1981).

In a study on the relationship between physical and chemical properties and carcinogenic activities of 18 nickel compounds at a standard 14-mg intramuscular dose of nickel under comparable experimental conditions in male Fischer 344 rats (see p. 321), five nickel sulfides were among the compounds tested. Three of these (α-nickel subsulfide, crystalline β-nickel sulfide and nickel ferrosulfide matte) induced local sarcomas in 100% of animals (9/9, 14/14 and 15/15). Metastases developed in 56, 71 and 67%, respectively, of the tumour-bearing rats. Nickel disulfide induced local tumours in 86% (12/14) animals and amorphous nickel sulfide in 12% (3/25). Median latent periods were 30 weeks for nickel subsulfide, 40 weeks for crystalline nickel sulfide, 36 weeks for nickel disulfide, 41 weeks for amporphous nickel sulfide, but only 16 weeks for nickel ferrosulfide. Median survival times were 39, 48, 47, 71 and 32 weeks, respectively (Sunderman, 1984).

In the study by Berry *et al.* (1984) described on p. 321, tumours developed in 10/20 rats given 5 mg nickel subsulfide intramuscularly, in 0/20 treated subperiosteally and in 10/20 given intrafemoral injections.

In the study by Judde *et al.* (1987) described on p. 321, a single intramuscular injection of 5 mg nickel subsulfide induced tumours in 2/100 rats.

[The Working Group was aware of several other studies in which nickel subsulfide was used as a positive control or as a model for the induction of rhabdomyosarcomas.]

Hamster: Groups of 15 or 17 male Syrian hamsters, two to three months of age, received a single intramuscular injection of 5 or 10 mg nickel subsulfide in 0.02-0.5 ml sterile saline. Of the 15 animals receiving the 5-mg dose, four developed local sarcomas, with a median latent period of ten months. At the 10-mg dose, 12/17 hamsters had local tumours, with a mean latency of 11 months [$p < 0.01$, trend test]. No tumour occurred among 14 controls injected with saline alone (Sunderman, 1983a).

Rabbit: Six-month-old white rabbits [sex and number unspecified] received intramuscular implants of agar-agar blocks containing approximately 80 mg nickel subsulfide powder. Sixteen rabbits with local tumours (rhabdomyosarcomas) were examined. Tumours were first observed about four to six months after implantation as small growths, which usually ceased active progression for up to 80 weeks then grew rapidly over the next four or five weeks (Hildebrand & Biserte, 1979a,b). [The Working Group noted the limited reporting of the study.]

Four male New Zealand albino rabbits, two months old, received bilateral intramuscular injections of 25 mg α-nickel subsulfide (50 mg/rabbit) in 0.1-0.5 ml penicillin G procaine suspension. All animals died between 16 and 72 months. No local tumour was found on autopsy (Sunderman, 1983a). [The Working Group noted the short observation period.]

(vi) *Intraperitoneal administration*

Rat: Of a group of 37 Fischer rats [sex and age unspecified] that received a single intraperitoneal injection of nickel subsulfide [dose unspecified], nine developed tumours, eight of which were rhabdomyosarcomas and one a mesothelioma (Gilman, 1966). [The Working Group noted the limited reporting of the study.]

A group of 50 female Wistar rats, 12 weeks of age, received a single intraperitoneal injection of 25 mg nickel subsulfide. Abdominal tumours (sarcomas, mesotheliomas and carcinomas) occurred in 27/42 animals, with an average latent period of eight months (Pott *et al.*, 1987).

In a study described above (p. 322), three doses of nickel subsulfide were injected into the peritoneal cavities of groups of female Wistar rats. Local tumours were observed at 30 months in 20/36 animals that received 6 mg (as Ni) as a single injection, in 23/35 receiving 12 mg (as Ni) as two 6-mg injections and in 25/34 given 25 mg (as Ni) as 25 1-mg injections. The tumours were mesotheliomas or sarcomas of the abdominal cavity (Pott *et al.*, 1989, 1990). [The Working Group noted that the results at 30 months were available as an extended abstract only.]

(vii) *Intrarenal administration*

Rat: Groups of 16 and 24 female Sprague-Dawley rats, weighing 120-140 g, received a single injection of 5 mg nickel subsulfide in 0.05 ml glycerine or 0.5 ml saline into each pole of the right kidney. Renal-cell carcinomas occurred in 7/16 and 11/24 animals compared with 0/16 in animals given 0.5 ml glycerine (Jasmin & Riopelle, 1976).

In a second experiment (Jasmin & Riopelle, 1976), the activity of other nickel compounds and divalent metals was investigated under identical experimental conditions using glycerine as the vehicle; all rats were autopsied after 12 months' exposure. In one group of 18 rats, nickel sulfide [probably amorphous] exhibited no

renal tumorigenic activity. [The Working Group noted that it was not stated whether crystalline or amorphous nickel sulfide was used.]

Groups of male and female Wistar Lewis, NIH black, Fischer 344 and Long-Evans rats, eight weeks of age, received an intrarenal injection of 5 mg α-nickel subsulfide. The incidence of malignant renal tumours 100 weeks after exposure was 7/11 in Wistar Lewis, 6/12 in NIH black, 9/32 in Fischer and 0/12 in Long-Evans rats. Groups of 11-24 male Fischer rats were given an intrarenal injection of 0.6, 1.2, 2.5, 5 or 10 mg nickel subsulfide; no tumour was seen with 0.6, 1.2 or 2.5 mg, but responses of 5/18 and 18/24 were obtained with 5 mg and 10 mg, showing a dose-response effect. All tumours were malignant, but the authors could not establish whether the tumours were of epithelial or mesenchymal origin; 70% had distant metastases (Sunderman *et al.*, 1979a).

Groups of male Fischer 344 rats [initial number unspecified], approximately eight weeks old, received an intrarenal injection of 7 mg nickel as one of several sulfides in 0.1 or 0.2 ml saline or in glycerol:distilled water (1:1, v/v) in each pole of the right kidney and were observed for two years after treatment. The incidence of renal cancer was significantly elevated in treated groups: nickel disulfide, 2/10 (fibrosarcomas); crystalline β-nickel sulfide, 8/14 (three fibrosarcomas, three other sarcomas, one renal-cell carcinoma, one carcinosarcoma); and α-nickel subsulfide, 4/15 (mesangial-cell sarcomas). Renal cancers occurred in 1/12 (sarcoma) rats treated with nickel ferrosulfide and in 0/15 rats treated with amorphous nickel sulfide. No local tumour developed in vehicle controls (Sunderman *et al.*, 1984b).

(viii) *Intratesticular administration*

Rat: A group of 19 male Fischer 344 rats, eight weeks of age, received an injection of 10 mg α-nickel subsulfide in 0.3 ml saline into the centre of the right testis and were observed for 20 months, at which time all the animals had died. A control group of 18 rats received an injection of 0.3 ml saline only, and a further two groups of four rats each received injections of either 10 mg metallic iron powder in saline or 2 mg zinc[II] as zinc chloride in distilled water. Of the nickel subsulfide-treated rats, 16/19 developed sarcomas in the treated testis, ten of which were fibrosarcomas, three malignant fibrous histiocytomas and three rhabdomyosarcomas. Four of the rats had distant metastases. No tumour occurred in the other groups (Damjanov *et al.*, 1978).

(ix) *Intraocular administration*

Rat: A group of 14 male and one female Fischer 344 rats, four weeks of age, received an injection of 0.5 mg α-nickel subsulfide in 20 μl saline into the vitreous cavity of the right eye under anaesthetic. Eleven male controls were similarly injected with saline alone. The experiment was terminated at 40-42 weeks after

treatment, when 11 control and one surviving treated rats were killed. Between 26 and 36 weeks after injection, 14/15 rats developed ocular tumours. Five of the tumorous eyes contained multiple neoplasms, and 22 distinct ocular tumours were identified as 11 melanomas, four retinoblastomas, three gliomas, one phakocarcinoma [lens capsular tumour] and three unclassified malignant tumours. No tumour developed in either the controls or in the uninjected, left eyes of treated rats. It was postulated that the very high incidence (93%) and short latent periods may have been due in part to the relative isolation of the vitreous bodies from the systemic circulation (blood-retina barrier), which would result in a high concentration of nickel[II]. The authors also pointed out that nickel particles within the vitreous body were relatively sequestered from phagocytosis. The visibility of developing tumours within the chamber permits their very early recognition (Albert *et al.*, 1980; Sunderman, 1983b).

Salamander: A group of eight lentectomized Japanese common newts received a single injection of 40-100 μg nickel subsulfide into the vitreous chamber of the eye under anaesthetic. Seven newts developed ocular melanoma-like tumours within nine months, while no tumour occurred in six controls injected with 2-3 μl sterile 0.6% saline or eye-dropper oil after lens extirpation. The lens regenerated in each of the control eyes. The site of tumour origin could not be determined, although it was suggested to be the iris, which showed numerous aberrant proliferating cells at three months (Okamoto, 1987).

(x) *Transplacental administration*

Rat: A group of eight pregnant female Fischer 344 rats, 120-150 days of age, received an intramuscular injection of 20 mg α-nickel subsulfide in 0.2 ml procaine penicillin G suspension on day 6 of gestation, allowing for gradual dissolution of the nickel subsulfide throughout the remainder of the pregnancy. A group of controls received an injection of vehicle only. No difference in the incidence of benign or malignant tumours was seen between the 50 pups born to treated dams and 53 control pups observed for 26 months (Sunderman *et al.*, 1981). [The Working Group noted that only one dose was used, which was not toxic to the fetuses.]

(xi) *Implantation into subcutaneously implanted tracheal grafts*

Rat: Groups of 30 and 32 female Fischer 344 rats, ten weeks of age, received five gelatin pellets containing 1 or 3 mg nickel subsulfide in heterotopic tracheal transplants inserted under the dorsal skin. At the lower dose level, tumours developed in 9/60 tracheas (six carcinomas and three sarcomas); at the higher dose level, tumours developed in 45/64 tracheas (one carcinoma and 44 sarcomas). No tumour developed in 20 control transplanted tracheas. The high dose resulted in necrosis of the epithelium and thus favoured the development of sarcomas (Yarita & Nettesheim, 1978).

(xii) *Intramuscular, subcutaneous or intra-articular injection or injection into retroperitoneal fat*

Rat: In a study designed to determine the types of sarcoma that develop from various mesenchymal tissue components, groups of 20 male Fischer 344 rats, seven to eight weeks of age, received injections of 5 mg nickel subsulfide either intramuscularly, subcutaneously, into the intra-articular space or into retroperitoneal fat. Control groups of ten rats each were injected with 0.5 ml aqueous procaine penicillin G vehicle. The incidences and types of sarcoma that developed in the experimental groups were: intramuscular, 19/20 (all rhabdomyosarcomas); subcutaneous, 18/19 (ten malignant fibrous histiocytomas, five rhabdomyosarcomas, three fibrosarcomas or unclassified); intra-articular, 16/19 (eight rhabdomyosarcomas, three malignant fibrous histiocytomas, five fibrosarcomas or unclassified); and retroperitoneal fat, 9/20 (five malignant fibrous histiocytomas, three rhabdomyosarcomas, one fibrosarcoma or unclassified). Controls did not develop tumours (Shibata *et al.*, 1989).

(xiii) *Administration with known carcinogens*

Rat: Groups of 30 male Fischer rats, eight to nine weeks of age, received intramuscular injections in both thighs of either 10 mg nickel subsulfide, 10 mg benzo[*a*]pyrene or 20 mg nickel subsulfide plus 10 mg benzo[*a*]pyrene in penicillin G procaine suspension, or vehicle alone. All treated rats developed sarcomas; rhabdomyosarcomas occurred in 24/30 given 10 mg nickel subsulfide, 4/30 given benzo[*a*]pyrene and 28/30 given 20 mg nickel subsulfide plus benzo[*a*]pyrene. No sarcoma occurred in controls (Maenza *et al.*, 1971).

Groups of 13, 13 and 12 male Wistar rats, weighing approximately 200 g, received single intratracheal injections of 5 mg nickel subsulfide, 2 mg benzo[*a*]pyrene or 5 mg nickel subsulfide plus 2 mg benzo[*a*]pyrene and were observed for 15 months. One rat from each group developed a tumour, consisting of one hepatoma, one retroperitoneal tumour and one squamous-cell carcinoma of the lung, respectively. Significant differences were seen in the incidence of preneoplastic lesions (peribronchial adenomatoid proliferation and bronchial squamous metaplasia), the occurrence decreasing in the order: nickel subsulfide plus benzo[*a*]pyrene > benzo[*a*]pyrene > nickel subsulfide (Kasprzak *et al.*, 1973).

(*d*) *Nickel salts*

(i) *Intramuscular administration*

Rat: A group of 32 male and female Wistar rats, two to three months of age, received an injection of 5 mg nickel sulfate hexahydrate in one or both thigh muscles (54 injected sites). Thirteen rats survived until the end of the experiment at 603 days.

No local tumour was found at the site of injection. No vehicle control was used (Gilman, 1962).

In a study reported as an abstract, sheep fat pellets, each containing 7 mg of either nickel sulfate, nickel chloride, nickel acetate, anhydrous nickel acetate, nickel carbonate or nickel ammonium sulfate, were given as three intramuscular implants [interval unspecified] into groups of 35 Bethesda black [NIH black] rats. Animals were observed for 18 months. Six tumours developed in the nickel carbonate group; single tumours developed in the nickel acetate and nickel sulfate groups. No tumour developed in any of the other groups or in 35 controls (Payne, 1964).

In a study comparing the in-vitro solubility and carcinogenicity of several nickel compounds, nickel fluoride and nickel sulfate were suspended in penicillin G procaine and injected intramuscularly [dose unspecified] into groups of 20 Fischer rats [sex and age unspecified]. The incidence of local sarcomas was 3/18 (17%; 3/36 sites) with nickel fluoride and 0/20 with nickel sulfate. Seventeen of 20 (85%) rats given nickel subsulfide as a positive control developed local sarcomas. No tumour developed in 20 rats injected with nickel sulfide [presumed to be amorphous] (Gilman, 1966). [The Working Group noted that no concurrent vehicle control was used and that the length of observation was not specified.]

A group of 20 male Wistar rats, weighing 200-220 g, received 15 intramuscular injections of 20 µl of a 0.2 M solution of nickel sulfate (4.4 µmol [0.26 mg]/injection of nickel; total dose, 66 µmol [4 mg]/rat nickel) every other day during one month. Further groups of 20 male rats received injections of nickel subsulfide (total dose, 40 µmol [7.1 mg nickel]; positive control) or sodium sulfate (15 injections of 20 µl of a 0.2 M solution; negative control). Nickel subsulfide induced local tumours in 16/20 rats; no tumour developed in nickel sulfate- or sodium sulfate-treated rats (Kasprzak *et al.*, 1983).

One local sarcoma was found in 16 male Fischer 344 rats, two to three months old, given an intramuscular injection of nickel chromate into the right thigh as 14 mg/rat nickel. Ten rats survived two years (Sunderman, 1984).

(ii) *Intraperitoneal administration*

Mouse: In a screening assay for lung adenomas in strain A mice, groups of ten male and ten female Strong strain A mice, six to eight weeks old, received intraperitoneal injections of nickel acetate in 0.85% physiological saline (total doses, 72, 180 and 360 mg/kg bw) three times a week for 24 weeks and were observed for 30 weeks, at which time all survivors were autopsied. Further groups of mice received a single intraperitoneal injection of 20 mg urethane (positive control), 24 injections of saline only or remained untreated. The incidences of lung tumours were: saline control, 37% (0.42 tumours/animal); untreated control, 31% (0.28 tumours/animal); positive control, 100% (21.6 tumours/animal); 72 mg nickel acetate, 44% (0.67 tumours/

animal); 180 mg nickel acetate, 50% (0.71 tumours/animal); and 360 mg nickel acetate, 63% (1.26 tumours/animal). The difference in response between the group given 360 mg nickel acetate and the negative control group was significant ($p < 0.01$). Five adenocarcinomas of the lung were observed in the nickel-treated mice compared to none in controls (Stoner *et al.*, 1976).

In the same type of screening assay, 30 male and female Strong strain A mice, six to eight weeks of age, received intraperitoneal injections of 10.7 mg/kg bw nickel acetate tetrahydrate (maximal tolerated dose; 0.04 mmol [2.4 mg]/kg bw nickel) three times a week for 24 weeks. A control group received injections of 0.9% saline under the same schedule. Animals were autopsied 30 weeks after the first injection. Of the nickel-treated group, 24/30 animals survived to 30 weeks and had an average of 1.50 lung adenomas/animal, whereas 25/30 controls had an average of 0.32 lung adenoma/animal ($p < 0.05$) (Poirier *et al.*, 1984).

Rat: In a study described earlier (p. 322), groups of female Wistar rats were given repeated intraperitoneal injections of 1 mg of each of four soluble nickel salts. The dose schedule and tumour responses at 30 months are shown in Table 23. The tumours were either mesotheliomas or sarcomas (tumours of the uterus were not included) (Pott *et al.*, 1989, 1990). [The Working Group noted that administration of nickel sulfate and nickel chloride by intramuscular injection has not been shown to induce tumours in rats. They suggest that in this instance the repeated small intraperitoneal doses permitted repeated exposure of potential target cells. Repeated intramuscular injections would result in nickel coming into contact with different cells at each injection. The Group also noted that the results at 30 months were reported only as an extended abstract.]

(iii) *Administration with known carcinogens*

Rat: Groups of 12 rats [strain, sex and age unspecified] received a single subcutaneous injection of 9 mg/ml dinitrosopiperazine in aqueous Tween 80. The following day, one group received topical insertion into the nasopharynx of 0.02 ml of a 0.5% solution of nickel sulfate in 4% aqueous gelatin once a week for seven weeks. A further group was held for six days and then administered 1 ml of aqueous 1% nickel sulfate solution in the drinking-water for six weeks. Additional groups of 12 rats received treatment with dinitrosopiperazine, nickel sulfate solution or nickel sulfate in gelatin only. Survival at 371 days was lower in the group treated with dinitropiperazine plus nickel sulfate solution in the drinking-water than in the group given the nitrosamine or the nickel sulfate solution alone. Two nasopharyngeal tumours (one squamous-cell carcinoma, one fibrosarcoma) occurred in the group treated with dinitropiperazine plus nickel sulfate in drinking-water and two (one papilloma, one early carcinoma) in the group treated with dinitropiperazine plus

Table 23. Tumour responses of rats to intraperitoneal injection of soluble nickel salts[a]

Compound	Total dose (mg, as Ni)	Schedule	Incidence of abdominal tumours
Nickel chloride.$6H_2O$	50	50 × 1 mg	4/32 [$p < 0.05$]
Nickel sulfate.$7H_2O$	50	50 × 1 mg	6/30 [$p < 0.05$]
Nickel acetate.$4H_2O$	25	25 × 1 mg	3/35
	50	50 × 1 mg	5/31 [$p < 0.05$ for trend]
Nickel carbonate	25	25 × 1 mg	1/35
Nickel hydroxide.$2H_2O$	50	50 × 1 mg	3/33
Saline		3 × 1 ml	1/33
		50 × 1 ml	0/34

[a]From Pott *et al.* (1989, 1990)

insertion of nickel sulfate in gelatin. No tumour occurred in the other groups. The authors concluded that 'probably nickel has a promoting action in the induction of nasopharyngeal carcinoma in rats following dinitrosopiperazine initiation' (Ou *et al.*, 1980). [The Working Group noted the small number of animals used and the poor survival.]

As reported in an abstract, in an extension of the study by Ou *et al.* (1980), five of 22 rats given an initiating injection of dinitrosopiperazine developed carcinomas following oral administration of nickel sulfate in gelatin. Two of the carcinomas were of the nasopharynx, two of the nasal cavity and one of the hard palate. No tumour developed in rats [numbers unspecified] treated with dinitrosopiperazine plus aqueous nickel sulfate, with nickel sulfate in gelatin alone or with dinitrosopiperazine alone (Liu *et al.*, 1983). [The Working Group noted the small number of animals used and the poor survival.]

As reported in an abstract, a group of 13 female rats [strain and age unspecified] received a single subcutaneous injection of 9 mg dinitrosopiperazine on day 18 of gestation. Pups of treated dams were fed 0.05 ml of 0.05% nickel sulfate beginning at four weeks of age every day for one month. The dose of nickel sulfate was increased by 0.1 ml per month for a further five months, by which time 5/21 pups had developed carcinomas of the nasal cavity. In a group of untreated pups of treated dams, 3/11 rats developed tumours (one nasopharyngeal squamous-cell carcinoma, one neurofibrosarcoma of the peritoneal cavity and one granulosa-thecal-cell carcinoma of the ovary). Groups given nickel sulfate and untreated control groups of seven pups each did not develop tumours. None of the pregnant rats that had been injected with dinitrosopiperazine alone developed tumours (Ou *et al.*, 1983).

Groups of 15 male Fischer 344 rats, seven weeks old, were administered 500 mg/l *N*-nitrosoethylhydroxyethylamine (NEHEA) in the drinking-water for two weeks. Thereafter, rats received drinking-water alone or drinking-water containing 600 mg/l nickel chloride hexahydrate for 25 weeks, when the study was terminated. The incidence of renal-cell tumours in the group receiving NEHEA and nickel chloride (8/15) was significantly higher ($p < 0.05$) than that in controls given NEHEA alone (2/15) or nickel chloride alone (0/15) (Kurokawa *et al.*, 1985). Nickel chloride did not show promoting activity in livers of Fischer 344 rats after initiation with *N*-nitrosodiethylamine, in gastric tissue of Wistar rats after initiation with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, in the pancreas of Syrian golden hamsters following initiation with *N*-nitrosobis(2-oxypropyl)amine or in skin of SENCAR mice initiated with 7,12-dimethylbenz[*a*]anthracene. The authors concluded that nickel chloride is a promoter in renal carcinogenesis in rats (Hayashi *et al.*, 1984; Kurokawa *et al.*, 1985).

(*e*) *Other nickel compounds*

(i) *Inhalation*

Rat: Groups of 64 or 32 male Wistar rats, weighing 200-250 g, were exposed by inhalation for 30 min to 30 or 60 mg/m^3 nickel carbonyl vapourized from a solution in 50:50 ethanol:diethyl ether, respectively, three times a week for 52 weeks. Another group of 80 rats was exposed once to 250 mg/m^3 nickel carbonyl. All treated animals had died by 30 months. One lung carcinoma appeared in each of the first two groups, and two pulmonary carcinomas developed in the last group. No pulmonary tumour occurred among 41 vehicle-treated control rats (Sunderman *et al.*, 1957, 1959). A further group of 285 rats was exposed for 30 min to 600 mg/m^3 nickel carbonyl; 214 died from acute toxicity. One lung adenocarcinoma was observed in the remaining 71 animals. Similar exposure to nickel carbonyl followed by intraperitoneal injection of sodium diethyl dithiocarbamate, an antidote, resulted in survival of all 60 treated rats and the development of a single anaplastic lung carcinoma. Minimal time to observation of lung tumours in these groups was in excess of 24 months. No lung carcinoma was observed in a group of 32 controls (Sunderman & Donnelly, 1965).

A group of five non-inbred rats [sex and age unspecified] was exposed by inhalation to 70 mg/m^3 nickel refinery dust (containing 11.3% metallic nickel, 58.3% nickel sulfide [identity unspecified], 1.7% nickel monoxide and 0.2% water-soluble nickel [composition of sample unclear]) for 5 h per day on five days per week for six months. Seventeen months after the start of treatment, one of five rats developed a squamous-cell carcinoma of the lung. No tumour developed among 47 untreated controls (Saknyn & Blokhin, 1978). [The Working Group noted the small number of animals used.]

Hamster: Groups of 102 male Syrian golden outbred LAK:LVG hamsters, two months old, were exposed by inhalation to concentrations of 17 or 70 mg/m^3 nickel-enriched fly ash from the addition of nickel acetate to pulverized coal before combustion (nickel content, 6%) for 6 h per day on five days per week for 20 months. Further groups were exposed to 70 mg/m^3 fly ash containing 0.3% nickel, or were sham-exposed. Five animals from each group were autopsied at four-month intervals up to 16 months, and all survivors were sacrificed at 20 months. No significant difference in mortality rate or body weight was observed between the groups. There were 14, 16, 16 and seven benign and malignant tumours in the sham-exposed, fly ash, low-dose and high-dose nickel-enriched fly ash groups, respectively. The only two malignant pulmonary neoplasms (one adenocarcinoma, one mesothelioma) occurred in the group receiving fly ash enriched with the high dose of nickel (Wehner *et al.*, 1981, 1984).

(ii) *Intratracheal instillation*

Rat: A group of 26 white non-inbred rats [sex and age unspecified] received a single intratracheal instillation of 20-40 mg aerosol dust (64.7% nickel monoxide (black), 0.13% nickel sulfide, 0.18% metallic nickel) in 0.6 ml saline. One squamous-cell carcinoma of the lung had developed by 17 months. No tumour developed among a group of 47 controls (Saknyn & Blokhin, 1978). [The Working Group noted that it was not stated whether the controls were untreated or received the vehicle alone.]

(iii) *Intramuscular administration*

Mouse: A group of 40 female Swiss mice, two to three months of age, received an intramuscular injection in each thigh of 10 mg of a nickel refinery dust (57% nickel subsulfide, 20% nickel sulfate hexahydrate, 6.3% nickel monoxide) suspended in penicillin G procaine. Of the 36 mice that survived more than 90 days, 20 developed a total of 23 local sarcomas, with an average latent period of 46 weeks. No tumour occurred among 48 control mice injected with the vehicle alone (Gilman & Ruckerbauer, 1962).

Rat: A group of 35 male and female hooded rats, two to three months of age, received an intramuscular injection in each thigh of 20 mg of a nickel refinery dust (57% nickel subsulfide, 20% nickel sulfate hexahydrate, 6.3% nickel oxide) suspended in penicillin G procaine. Of the 27 rats that survived more than 90 days, 19 developed local sarcomas. Another group of 31 male and female rats received injections of the same refinery dust after repeated washing in distilled water; 20/28 of the rats that survived more than 90 days developed local tumours at one or other of the injection sites. No tumour occurred among 30 control rats injected with the vehicle alone (Gilman & Ruckerbauer, 1962).

Groups of 25 male and 25 female Fischer 344 rats [age unspecified] received 12 intramuscular injections of 12 or 25 mg nickelocene in trioctanoin. Tumour incidences were 18/50 and 21/50, respectively. No local tumour occurred in a group of 25 male and 25 female controls (Furst & Schlauder, 1971).

Groups of 15-30 male Fischer 344 rats, approximately eight weeks old, received a single intramuscular injection of 14 mg nickel as one of four nickel arsenides, nickel antimonide, nickel telluride, nickel sinter matte (Ni_4FeS_4; positive control), nickel titanate or ferronickel alloy ($NiFe_{1-6}$; negative controls) in 0.3 ml glycerol:water (1:1; v/v) into the exterior thigh. The compounds were >99.9% pure and were ground down to a median particle size of <2 μm. Rats that died within two months of the injection were excluded from the experiment; remaining animals were observed for two years. Median survival ranged from 32 weeks (positive controls) to over 100 weeks (negative controls). The incidences of local tumours in the groups were: nickel sinter matte, 15/15; nickel sulfarsenide, 14/16; nickel arsenide hexagonal, 17/20; nickel antimonide, 17/29; nickel telluride, 14/26; and nickel arsenide tetragonal, 8/16. No tumour was observed in the groups treated with nickel arsenide, ferronickel alloy or nickel titanate nor in a vehicle control group. Median latency for tumour induction ranged from 16 weeks (positive controls) to 33 weeks (nickel arsenide tetragonal-treated group). The incidence of tumours induced by the test compounds was significantly greater than that in the vehicle control group ($p < 0.001$); 67% of all the sarcomas were rhabdomyosarcomas, 11% fibrosarcomas, 15% osteosarcomas and 5% undifferentiated sarcomas. Metastases occurred in 57% of tumour-bearing rats (Sunderman & McCully, 1983).

In a continuation of these tests, nickel selenide, nickel subselenide and nickel monoxide (positive control; see p. 327) were tested using the same experimental techniques. Nickel selenide and nickel subselenide induced significant increases in the incidence of local tumours (8/16 and 21/23, respectively; $p < 0.001$); the positive control group had 14/15 tumours. Metastases occurred in 38 and 86%, respectively, of tumour-bearing rats in the selenium-treated groups and in 29% of positive controls. Approximately 50% of the tumours were rhabdomyosarcomas (Sunderman, 1984).

Hamster: Groups of 25 male and 25 female hamsters, three to four weeks old, received eight monthly injections of 5 mg nickelocene in 0.2 ml trioctanoin into the right thigh. No tumour was induced. A group of survivors from another test [age unspecified] received a single intramuscular injection of 25 mg nickelocene in trioctanoin; fibrosarcomas occurred in 1/13 females and 3/16 males. No tumour occurred in 25 male or 25 female vehicle controls (Furst & Schlauder, 1971).

(iv) *Intraperitoneal administration*

Rat: Groups of 16 and 23 non-inbred albino rats [sex and age unspecified] received a single intraperitoneal injection of 90-150 mg of one of two refinery dusts: the first contained 11.3% metallic nickel, 58.3% nickel sulfide, 1.7% nickel monoxide and 0.2% water-soluble nickel; the second contained 2.9% metallic nickel, 26.8% nickel sulfide, 6.8% nickel monoxide and 0.07% water-soluble nickel. Each was given in 1.5 ml physiological saline. Three local sarcomas developed within six to 15 months in animal treated with the first dust, and three local sarcomas developed within nine to 11 months in animals treated with the second dust. No tumour was observed in 47 control rats (Saknyn & Blokhin, 1978). [The Working Group noted that it was not specified whether control rats were untreated or were treated with the vehicle.]

(v) *Intravenous administration*

Rat: A group of 61 male and 60 female Sprague-Dawley rats, eight to nine weeks of age, received six injections of 9 mg/kg bw nickel carbonyl (as Ni) at two- to four-week intervals and were observed for life. Nineteen animals developed malignancies, six of which were undifferentiated sarcomas and three, fibrosarcomas at various sites; the other tumours were single carcinomas of the liver, kidney and mammary gland, one haemangioendothelioma, one undifferentiated leukaemia and five pulmonary lymphomas. Two pulmonary lymphomas developed in 15 male and 32 female sham-injected controls. The difference in total tumour incidence was significant ($p < 0.05$) (Lau *et al.*, 1972).

(vi) *Intrarenal administration*

Groups of male fischer rats [initial number unspecified], approximately eight weeks old, received intrarenal injections of 7 mg nickel as one of several nickel compounds in 0.1 or 0.2 ml saline solution or in glycerol:distilled water (1:1, v/v) in each pole of the right kidney and were observed for two years after treatment. The incidence of renal cancer was significantly elevated in the groups treated with nickel sulfarsenide (3/15 sarcomas) but not in those treated with nickel arsenide (1/20 renal-cell carcinoma), nickel selenide (1/12 sarcoma), nickel subselenide (2/23 sarcomas), nickel telluride (0/19), nickel subarsenides (tetragonal and hexagonal; 0/15 and 0/17), nickel antimonide (0/20) or nickel titanate (0/19). No local tumour developed in vehicle controls (Sunderman *et al.*, 1984b).

The experiments described in section 3.1 are summarized in Table 24.

Table 24. Summary of studies used to evaluate the carcinogenicity to experimental animals of metallic nickel and nickel compounds

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Metallic nickel powder and nickel alloys				
Cr/Ni stainless steel	Intratracheal	Hamster (60)	36 mg, no local tumour 108 mg, no local tumour	Muhle *et al.* (1990)
Metallic nickel powder	Inhalation	Mouse (20)	No lung tumour	Hueper (1958)
Metallic nickel powder	Inhalation	Rat (160)	Benign lung neoplasms	Hueper (1958)
Metallic nickel powder (plus sulfur dioxide)	Inhalation	Rat (120)	0/46 lung tumour	Hueper & Payne (1962)
Metallic nickel powder	Inhalation	Guinea-pig (42)	1/23 intra-alveolar carcinoma, 1/23 metastasis of adenocarcinoma	Hueper (1958)
Metallic nickel powder	Intratracheal	Rat (80)	10. × 0.9 mg, 8/32 lung tumours [$p < 0.05$] 20 × 0.3 mg, 10/39 lung tumours [$p < 0.05$] Controls, 0/40 lung tumour	Pott *et al.* (1987)
Metallic nickel powder	Intratracheal	Hamster (100 per group)	10 mg, 1% local tumours 20 mg, 8% local tumours 40 mg, 12% local tumours 4 × 20 mg, 10% local tumours	Ivankovic *et al.* (1987)
Metallic nickel powder	Intratracheal	Hamster (60)	1/56 lung tumour	Muhle *et al.* (1990)
Metallic nickel powder	Intrapleural	Rat (25)	4/12 local sarcomas *vs* 0/70 in controls [$p < 0.01$]	Hueper (1952)
Metallic nickel powder	Intrapleural	Rat (10)	2/10 mesotheliomas *vs* 0/20 in controls	Furst *et al.* (1973)
Metallic nickel powder	Subcutaneous	Rat (10)	5/10 local tumours	Mitchell *et al.* (1960)
Metallic nickel powder	Intramuscular	Rat (10)	10/10 local tumours *vs* 0 in controls	Heath & Daniel (1964)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Metallic nickel powder	Intramuscular	Rat (50)	38/50 local tumours *vs* 0 in controls	Furst & Schlauder (1971)
Metallic nickel powder	Intramuscular	Rat (20)	3.6 mg, 0/10 local tumours 14.4 mg, 2/9 local tumours Controls, 0/20 local tumours	Sunderman & Maenza (1976)
Metallic nickel powder	Intramuscular	Rat (20)	17/20 local tumours *vs* 0/56 in controls	Berry *et al.* (1984)
Metallic nickel powder	Intramuscular	Rat (20)	13/20 local tumours *vs* 0/44 in controls	Sunderman (1984)
Metallic nickel powder	Intramuscular	Rat (40)	14/30 local tumours *vs* 0/60 in controls	Judde *et al.* (1987)
Metallic nickel powder	Intramuscular	Hamster (50)	2/50 local tumours *vs* 0/50 in controls	Furst & Schlauder (1971)
Metallic nickel powder	Intraperitoneal	Rat	30–50% local tumours *vs* none in controls	Furst & Cassetta (1973)
Metallic nickel powder	Intraperitoneal	Rat (50)	46/48 abdominal tumours	Pott *et al.* (1987)
Metallic nickel powder	Intraperitoneal	Rat	6 mg, 4/34 local tumours 2×6 mg, 5/34 local tumours 25×1 mg, 25/35 local tumours	Pott *et al.* (1990)
Metallic nickel powder	Intravenous	Mouse (25)	No tumour	Hueper (1955)
Metallic nickel powder	Intravenous	Rat (25)	7/25 local tumours	Hueper (1955)
Metallic nickel powder	Intrarenal	Rat (20)	No local tumour	Jasmin & Riopelle (1976)
Metallic nickel powder	Intrarenal	Rat	No local tumour	Sunderman *et al.* (1984b)
Metallic nickel powder	Subperiosteal	Rat (20)	11/20 local tumours	Berry *et al.* (1984)
Metallic nickel powder	Intrafemoral	Rat (20)	9/20 local tumours	Berry *et al.* (1984)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel alloy: 26.8%, Ni, 16.2% Cr, 39.2% Fe, 0.04% Co	Intratracheal	Hamster (100 per group)	10 mg, no local tumour 20 mg, no local tumour 40 mg, no local tumour 4×20 mg, no local tumour	Ivankovic *et al.* (1987)
Nickel alloy: 66.5%, Ni, 12.8% Cr, 6.5% Fe, 0.2% Co	Intratracheal	Hamster (100 per group)	10 mg, 1% local tumours 20 mg, 8% local tumours 40 mg, 12% local tumours 4×20 mg, 10% local tumours	Ivankovic *et al.* (1987)
Nickel-gallium alloy (60% Ni)	Subcutaneous	Rat (10)	9/10 local tumours	Mitchell *et al.* (1960)
Nickel-iron alloy ($NiFe_{1-8}$)	Intramuscular	Rat (16)	0/16 local tumours	Sunderman (1984)
Nickel-iron alloy ($NiFe_{1-8}$)	Intrarenal	Rat	1/14 renal cancers *vs* 0/46 controls	Sunderman *et al.* (1984b)
Nickel alloy (50% Ni)	Intraperitoneal	Rat	50 mg, 8/35 local tumours 3×50 mg, 13/35 local tumours	Pott *et al.* (1989, 1990)
Nickel alloy (29% Ni)	Intraperitoneal	Rat	50 mg, 2/33 local tumours 2×50 mg, 1/36 local tumours	Pott *et al.* (1989, 1990)
Nickel alloy (66% Ni)	Intraperitoneal	Rat	50 mg, 12/35 local tumours 3×50 mg, 22/33 local tumours	Pott *et al.* (1989, 1990)
Pentlandite	Intratracheal	Hamster (60)	1/60 local tumour	Muhle *et al.* (1990)
Nickel oxides and hydroxides				
Nickel monoxide (green)	Inhalation	Rat (6, 8)	8 mg/m³, 1/8 lung tumour 0.6 mg/m³, 0/6 lung tumour	Horie *et al.* (1985)
Nickel monoxide	Inhalation	Rat (40, 20)	0.06 mg/m³, no tumour 0.2 mg/m³, no tumour	Glaser *et al.* (1986)
Nickel monoxide	Inhalation	Hamster (51)	1/51 osteosarcoma	Wehner *et al.* (1975, 1979)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel monoxide	Intrapleural	Rat (32)	31/32 local tumours *vs* 0/32 in controls	Skaug *et al.* (1985)
Nickel monoxide	Intratracheal	Rat	10×5 mg, 10/37 lung tumours 10×15 mg, 12/38 lung tumours controls, 0/40	Pott *et al.* (1987)
Nickel monoxide	Intratracheal	Hamster (50)	1/49 lung tumours *vs* 4/50 in controls	Farrell & Davis (1974)
Nickel monoxide	Intramuscular	Mouse (50, 52)	33/50 and 23/52 local tumours	Gilman (1962)
Nickel monoxide	Intramuscular	Rat (32)	21/32 local tumorus	Gilman (1962)
Nickel monoxide	Intramuscular	Rat (20)	2/20 local tumours	Gilman (1966)
Nickel monoxide	Intramuscular	Rat (20)	No local tumour	Sosiński (1975)
Nickel monoxide	Intramuscular	Rat (15)	14/15 local tumours	Sunderman & McCully (1983)
Nickel monoxide	Intramuscular	Rat (20)	0/20 local tumour	Berry *et al.* (1984)
Nickel monoxide	Subperiosteal	Rat (20)	0/20 local tumour	Berry *et al.* (1984)
Nickel monoxide	Intraperitoneal	Rat (50)	46/47 local tumours	Pott *et al.* (1987)
Nickel monoxide	Intraperitoneal	Rat	25 mg, 12/34 local tumours 100 mg, 15/36 local tumours	Pott *et al.* (1989, 1990)
Nickel monoxide (green)	Intrarenal	Rat (12)	0/12 local tumour	Sunderman *et al.* (1984b)
Nickel hydroxide	Intramuscular	Rat	15/20 local tumours	Gilman (1966)
Nickel hydroxide	Intramuscular	Rat (3 x 20)	Dried gel: 5/19 local tumours Crystalline: 3/20 local tumours Colloidal: 0/13 local tumour	Kasprzak *et al.* (1983)
Nickel trioxide	Intramuscular	Rat (10)	0/10 local tumour	Judde *et al.* (1987)
Nickel trioxide	Intracerebral	Rat (20)	3/20 local tumours	Sosiński (1975)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel sulfides				
Nickel disulfide	Intramuscular	Rat	12/14 local tumours	Sunderman (1984)
Nickel disulfide	Intrarenal	Rat	2/10 local tumours	Sunderman *et al.* (1984b)
Nickel sulfide (amorphous)	Intramuscular	Rat (10 per group)	5.6 mg, no local tumour 22.4 mg, no local tumour	Sunderman & Maenza (1976)
β-Nickel sulfide	Intramuscular	Rat	14/14 local tumours	Sunderman (1984)
Nickel sulfide (amorphous)	Intramuscular	Rat	3/25 local tumours	Sunderman (1984)
Nickel sulfide	Intrarenal	Rat (18)	0/18 local tumour	Jasmin & Riopelle (1976)
β-Nickel sulfide	Intrarenal	Rat	8/14 local tumours	Sunderman *et al.* (1984b)
Nickel sulfide (amorphous)	Intrarenal	Rat	0/15 local tumour	Sunderman *et al.* (1984b)
Nickel subsulfide	Inhalation	Rat (226)	14/208 malignant lung tumours; 15/208 benign lung tumours	Ottolenghi *et al.* (1974)
Nickel subsulfide	Intratracheal	Mouse (100)	No increase in lung tumours	Fisher *et al.* (1986)
Nickel subsulfide	Intratracheal	Rat	0.94 mg: 7/47 lung tumours 1.88 mg: 13/45 lung tumours 3.75 mg: 12/40 lung tumours	Pott *et al.* (1987)
α-Nickel subsulfide	Intratracheal	Hamster (62)	0/62 lung tumour	Muhle *et al.* (1990)
Nickel subsulfide	Intrapleural	Rat (32)	28/32 local tumours	Skaug *et al.* (1985)
Nickel subsulfide	Subcutaneous	Mouse (20)	5 mg, 4/8 local tumours 10 mg, 7/8 local tumours	Oskarsson *et al.* (1979)
Nickel subsulfide	Subcutaneous	Rat (40 per group)	3.3 mg, 37/39 local tumours 10 mg, 37/40 local tumours	Mason (1972)
Nickel subsulfide	Subcutaneous	Rat (20)	18/19 local tumours	*Shibata et al. (1989)*

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel subsulfide	Intramuscular	Mouse (45, 18)	Swiss, 27/45 local tumours C3H, 9/18 local tumours	Gilman (1962)
Nickel subsulfide	Intramuscular	Mice (20)	5 mg, 4/8 local tumours 10 mg, 4/8 local tumours	Oskarsson *et al.* (1979)
Nickel subsulfide	Intramuscular	Mouse (10, 10)	C57Bl6, 5/10 local tumours DBA/2, 6/10 local tumours	Sunderman (1983b)
Nickel subsulfide	Intramuscular	Rat (32)	25/28 local tumours	Gilman (1962)
Nickel subsulfide	Intramuscular	Rat (20)	10 mg powder, 19/20 local tumours 500 mg fragments, 5/7 local tumours 500 mg discs, 14/17 local tumours 10 mg diffusion chamber, 14/17 local tumours controls, 1/19 local tumour	Gilman & Herchen (1963)
Nickel subsulfide (disc)	Intramuscular	Rat (groups of 15)	4/10 local tumours with removal of disc after 64 days 7/10 local tumours with removal of disc after 128 days 10/10 local tumours with removal of disc after 206 days	Herchen & Gilman (1964)
Nickel subsulfide	Intramuscular	Rat (30, 27)	NIH black, 28/28 local tumours Hooded, 14/23 local tumours	Daniel (1966)
Nickel subsulfide	Intramuscular	Rat (40 per group)	3.3 mg, 38/39 local tumours 10 mg, 34/40 local tumours	Mason (1972)
Nickel subsulfide	Intramuscular	Rat (10 per group)	5 mg, 8/20 local tumours 20 mg, 9/9 local tumours	Sunderman & Maenza (1976)
Nickel subsulfide	Intramuscular	Rat (63,20)	Fischer, 59/63 local tumours Hooded, 11/20 local tumours	Yamashiro *et al.* (1980)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel subsulfide	Intramuscular	Rats (groups of 30)	0.6 mg, 7/30 local tumours 1.2 mg, 23/30 local tumours 2.5 mg, 28/30 local tumours 5 mg, 29/30 local tumours	Sunderman *et al.* (1976)
Nickel subsulfide	Intramuscular	Rat	0.63 mg, 7/29 local tumours 20 mg, 9/9 local tumours	Sunderman (1981)
α-Nickel subsulfide	Intramuscular	Rat	9/9 local tumours	Sunderman (1984)
Nickel subsulfide	Intramuscular	Rat (20)	10/20 local tumours	Berry *et al.* (1984)
Nickel subsulfide	Intramuscular	Rat (100)	2/100 local tumours	Judde *et al.* (1987)
Nickel subsulfide	Intramuscular	Hamster (15, 17)	5 mg, 4/15 local tumours 10 mg, 12/17 local tumours controls, 0/14 local tumour	Sunderman (1983a)
Nickel subsulfide	Intramuscular	Rabbit	16 local tumours	Hildebrand & Biserte (1979a,b)
α-Nickel subsulfide	Intramuscular	Rabbit (4)	0/4 local tumour	Sunderman (1983a)
Nickel subsulfide	Intramuscular	Rat (20)	19/20 local tumours	Shibata *et al.* (1989)
α-Nickel subsulfide	Topical	Hamster (6–7, 13–15)	54 mg total, 0/6 local tumour; 108 mg total, 0/7 local tumour; 540 mg total, 0/15 local tumour; 1080 mg total, 0/13 local tumour	Sunderman (1983b)
Nickel subsulfide	Intraperitoneal	Rat (37)	9/37 local tumours	Gilman (1966)
Nickel subsulfide	Intraperitoneal	Rat (50)	27/42 local tumours	Pott *et al.* (1987)
Nickel subsulfide	Intraperitoneal	Rat	6 mg, 20/36 local tumours 12 mg, 23/35 local tumours 25 mg, 25/34 local tumours	Pott *et al.* (1989, 1990)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel subsulfide	Subperiosteal	Rat (20)	0/20 local tumour	Berry *et al.* (1984)
Nickel subsulfide	Intrafemoral	Rat (20)	10/20 local tumours	Berry *et al.* (1984)
Nickel subsulfide	Intrarenal	Rat (16/24)	In glycerin, 7/16 local tumours In saline, 11/24 local tumours	Jasmin & Riopelle (1976)
α-Nickel subsulfide	Intrarenal	Rat (11–32)	Wistar Lewis, 7/11 local tumours NIH black, 6/12 local tumours Fischer 344, 9/32 local tumours Long–Evans, 0/12 local tumour	Sunderman *et al.* (1979a)
Nickel subsulfide	Intratesticular	Rat (19)	16/19 local tumours	Damjanov *et al.* (1978)
Nickel subsulfide	Intraocular	Rat (15)	14/15 local tumours	Albert *et al.* (1980); Sunderman (1983b)
Nickel subsulfide	Intraocular	Salamander (8)	7/8 local tumours	Okamoto (1987)
Nickel subsulfide	Transplacental	Rat (8)	No difference in tumour incidence	Sunderman *et al.* (1981)
Nickel subsulfide	Pellet implantation into subcutaneous implanted tracheal grafts	Rat (60, 64)	5 mg, 9/60 local tumours 15 mg, 45/64 local tumours	Yarita & Nettesheim (1978)
Nickel subsulfide	Intra-articular	Rat (20)	16/19 local tumours	Shibata *et al.* (1989)
Nickel subsulfide	Intra-fat	Rat (20)	9/20 local tumours	Shibata *et al.* (1989)
Nickel ferrosulfide	Intramuscular	Rat	15/15 local tumours	Sunderman (1984)
Nickel ferrosulfide	Intrarenal	Rat	1/12 local tumour	Sunderman *et al* (1984b)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel salts				
Basic nickel carbonate tetrahydrate	Intraperitoneal	Rat	25 mg, 1/35 lung tumours *vs* 1/33 in controls 50 mg, 3/33 lung tumours *vs* 1/33 in controls	Pott *et al.* (1989, 1990)
Nickel acetate	Intramuscular	Rat (35)	1/35 local tumour	Payne (1964)
Nickel acetate	Intraperitoneal	Mouse (3 x 20)	72 mg, 8/18 lung tumours 180 mg, 7/14 lung tumours 360 mg, 12/19 lung tumours	Stoner *et al.* (1976)
Nickel acetate tetrahydrate	Intraperitoneal	Mouse (30)	1.50 lung tumours/animal Controls, 0.32 lung tumours/animal	Poirier *et al.* (1984)
Nickel acetate tetrahydrate	Intraperitoneal	Rat	25 mg, 3/35 lung tumours *vs* 1/33 in controls 50 mg, 5/31 lung tumours *vs* 1/33 in controls	Pott *et al.* (1989, 1990)
Nickel ammonium sulfate	Intramuscular	Rat (35)	0/35 local tumour	Payne (1964)
Nickel carbonate	Intramuscular	Rat (35)	6/35 local tumours	Payne (1964)
Nickel chloride	Intramuscular	Rat (35)	0/35 local tumour	Payne (1964)
Nickel chloride hexahydrate	Intraperitoneal	Rat	4/32 lung tumours *vs* 1/33 in controls	Pott *et al.* (1989, 1990)
Nickel chromate	Intramuscular	Rat (16)	1/16 local tumour	Sunderman (1984)
Nickel fluoride	Intramuscular	Rat (20)	3/18 local tumours	Gilman (1966)
Nickel sulfate	Intramuscular	Rat (35)	1/35 local tumour	Payne (1964)
Nickel sulfate	Intramuscular	Rat (20)	0/20 local tumour	Gilman (1966)
Nickel sulfate	Intramuscular	Rat (20)	0/20 local tumour	Kasprzak *et al.* (1983)
Nickel sulfate hexahydrate	Intramuscular	Rat (32)	0/32 local tumour	Gilman (1962)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel sulfate heptahydrate	Intraperitoneal	Rat	6/30 lung tumours *vs* 1/33 in controls	Pott *et al.* (1989, 1990)
Other nickel compounds				
Ferronickel alloy	Intramuscular	Rat	No local tumour	Sunderman & McCully (1983)
Nickel antimonide	Intramuscular	Rat	17/29 *vs* 0/40 control ($p < 0.05$)	Sunderman & McCully (1983)
Nickel antimonide	Intrarenal	Rat	0/20 local tumour	Sunderman *et al.* (1984b)
Nickel arsenide	Intramuscular	Rat	No local tumour	Sunderman & McCully (1983)
Nickel arsenide	Intrarenal	Rat	1/20 local tumour	Sunderman *et al.* (1984b)
Nickel arsenide hexagonal	Intramuscular	Rat	17/20 *vs* 0/40 controls ($p < 0.05$)	Sunderman & McCully (1983)
Nickel arsenide hexagonal	Intrarenal	Rat	0/17 local tumour	Sunderman *et al.* (1984b)
Nickel arsenide tetragonal	Intramuscular	Rat	8/16 *vs* 0/40 control ($p < 0.05$)	Sunderman & McCully (1983)
Nickel arsenide tetragonal	Intrarenal	Rat	0/15 local tumour	Sunderman *et al.* (1984b)
Nickel carbonyl	Inhalation	Rat (64, 32, 80)	30 mg/m³ for 32 weeks: 1/64 pulmonary tumour 60 mg/m³ for 32 weeks: 1/32 pulmonary tumour 250 mg/m³ once: 1/80 pulmonary tumour	Sunderman *et al.* (1957, 1959)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel carbonyl	Inhalation	Rat	1/71 lung tumour *vs* 0/32 control	Sunderman & Donnelly (1965)
Nickel carbonyl	Intravenous	Rat (121)	19/120 lung tumours	Lau *et al.* (1972)
Nickel-enriched fly ash	Inhalation	Hamster (102)	No significant difference	Wehner *et al.* (1981, 1984)
Nickelocene	Intramuscular	Rat (50)	144 mg, 18/50 local tumours 300 mg, 21/50 local tumours	Furst & Schlauder (1971)
Nickelocene	Intramuscular	Hamster (50)	8×5 mg, 0/50 local tumour 25 mg, 4/29 local tumours	Furst & Schlauder (1971)
Nickel monoxide dust	Intratracheal	Rat (26)	1/26 lung tumour *vs* 0/47 control	Saknyn & Blokhin (1978)
Nickel selenide	Intramuscular	Rat	8/16 local tumours	Sunderman (1984)
Nickel selenide	Intramuscular	Rat	1/12 local tumour *vs* 0/79 control	Sunderman *et al.* (1984b)
Nickel subselenide	Intramuscular	Rat	21/23 local tumours	Sunderman (1984)
Nickel subselenide	Intrarenal	Rat	2/23 local tumours *vs* 0/79 control	Sunderman *et al.* (1984b)
Nickel sulfarsenide	Intramuscular	Rat	14/16 *vs* 0/40 control ($p < 0.05$)	Sunderman & McCully (1983)
Nickel sulfarsenide	Intrarenal	Rat	3/15 local tumours *vs* 0/79 control	Sunderman *et al* (1984b)
Nickel telluride	Intramuscular	Rat	14/26 *vs* 0/40 control ($p < 0.05$)	Sunderman & McCully (1983)
Nickel telluride	Intrarenal	Rat	0/19 local tumour	Sunderman *et al.* (1984b)
Nickel titanate	Intramuscular	Rat	No local tumour	Sunderman & McCully (1983)

Table 24 (contd)

Compound	Route	Species (No. at start)	Tumour incidence (no. of animals with tumours/effective number)	Reference
Nickel titanate	Intrarenal	Rat	0/19 local tumour	Sunderman *et al.* (1984b)
Refinery dust	Inhalation	Rat (5)	1/5 lung tumour *vs* 0/47 control	Saknyn & Blokhin (1978)
Refinery dust	Intramuscular	Mouse (40)	20/36 local tumours *vs* 0/48 control ($p < 0.01$)	Gilman & Ruckerbauer (1962)
Refinery dust	Intramuscular	Rat (35)	Dust, 19/27 local tumours Washed dust, 20/28 local tumours Controls, 0/30 local tumour	Gilman & Ruckerbauer (1962)
Refinery dust	Intraperitoneal	Rat (16, 23)	Dust 1, 3/16 local tumours Dust 2, 3/23 local tumours Controls, 0/47 local tumour	Saknyn & Blokhin (1978)

3.2 Other relevant data in experimental systems

(a) *Absorption, distribution, excretion and metabolism*

The results of studies on absorption, distribution, excretion, and metabolism of nickel compounds have been reviewed and/or summarized in several publications (National Research Council, 1975; Sunderman, 1977; Kasprzak, 1978; Bencko, 1983; Mushak, 1984; Sarkar, 1984; Fairhurst & Illing, 1987; Kasprzak, 1987; Sunderman, 1988; Maibach & Menné, 1989).

(i) *Nickel oxides and hydroxides*

Male Wistar rats were exposed to 0.4-70 mg/m^3 (0.6-4-μm particles) nickel monoxide aerosols for 6-7 h per day on five days per week for a maximum of three months. The clearance rate of nickel monoxide from the lung after a one-month exposure to 0.6-8 mg/m^3 (1.2-μm particles) was estimated to be about 100 μg per year. The exposure did not increase background nickel levels in organs other than the lung (Kodama *et al.*, 1985).

Electron microscopic examination of the lungs of male Wistar rats exposed to nickel monoxide aerosols (0.6-8 mg/m^3; 1.2- or 2.2-μm particles) for a total of 140-216 h showed that the particles were trapped mainly by alveolar macrophages. One year after termination of exposure, the particles were distributed in the alveoli, hilar lymphoid apparatus and terminal bronchioli. Some nickel monoxide particles were present within the lysosomes of macrophages (Horie *et al.*, 1985).

Female Wistar rats were given a single intratracheal injection of black nickel monoxide, prepared by heating nickel hydroxide at 250°C for 45 min (final product containing a mixture of nickel monoxide and nickel hydroxide; > 90% insoluble in water; particles, 3.7 μm or less in diameter) in a normal saline suspension (100 nmol [7.5 μg] nickel monoxide in 0.2 ml). The highest concentrations of nickel were seen in the lungs and mediastinal lymph nodes, followed by the heart, femur, duodenum, kidney, pancreas, ovaries, spleen, blood and other tissues. Following injection, the concentration of nickel in the lung decreased at a much slower rate than in other tissues. By the third day after injection of nickel monoxide, about 17% of the nickel was excreted with the faeces and about 16% in the urine. By 90 days, about 60% of the dose of nickel had been excreted, half of it in the urine. The overall pattern indicates a partial transfer of nickel from lung to the mediastinal lymph nodes and slow solubilization of this product in tissue fluids (English *et al.*, 1981).

(ii) *Nickel subsulfide*

After intratracheal instillation of 11.7 μg α-^{63}Ni-nickel subsulfide powder (1-66-μm particles) in a normal saline suspension to male strain A/J mice, 38% was cleared from the lungs with a half-time of 1.2 days, while 42% was cleared with a

half-time of 12.4 days; 10% of the dose was retained in the lung 35 days after instillation. The highest amounts of nickel were found in the kidney, followed by blood > liver > femur up to seven days; at 35 days, levels were greatest in kidney, followed by femur > liver > blood; maximal levels occurred 4 h after dosing and decreased rapidly thereafter with biological half-times similar to those in the lung. The urine was the primary excretion pathway; after 35 days, 100% of the nickel dose was recovered in the excreta, 60% of which was in urine (Valentine & Fisher, 1984).

The cumulative eight-week urinary excretion of nickel following intramuscular injection of ^{63}Ni-nickel subsulfide to male Fischer rats (1.2 mg/rat, 1.4-μm particles) was 67%, while faecal excretion during that time was only 7% of the dose. The residual nickel contents at the injection site at 22 and 31 weeks after injection were 13-17% and 13-14% of the dose, respectively. The kinetics of nickel disappearance were described by a three-compartmental model, with pool sizes of 60, 27 and 11% of the dose and half-times of 14, 60 and indefinite number of days, respectively (Sunderman *et al.*, 1976).

α-Nickel subsulfide particles labelled with ^{63}Ni and ^{35}S injected intramuscularly into Fischer rats (Kasprzak, 1974) or intramuscularly and subcutaneously into NMRI mice of each sex (Oskarsson *et al.*, 1979) persisted at the injection site for several months, with a gradual loss of both ^{63}Ni and ^{35}S. In mice, nickel subsulfide was transferred to regional lymph nodes and to the reticuloendothelial cells of the liver and spleen. The presence of ^{63}Ni in the kidney and ^{35}S in the cartilage indicated solubilization of the subsulfide from the site of injection during tumorigenesis. There was no excessive or specific localization of the solubilized ^{63}Ni or ^{35}S in the tumours or in metastases. Most of the radioactivity in the tumours appeared to be associated with dust particles.

Elevated concentrations of nickel were detected in fetuses after intramuscular administration of α-nickel subsulfide to Fischer rats on day 6 of gestation (Sunderman *et al.*, 1978a).

(iii) *Nickel salts*

Intratracheal instillation of nickel chloride (100 nmol[13 μg]/rat) to female Wistar rats resulted in a fast distribution of nickel throughout the body, followed by rapid clearance. During the first six days after injection, over 60% of the dose was excreted in the urine and approximately 5% in faeces; after 90 days, these amounts had increased only slightly, to 64% and 6%, respectively (English *et al.*, 1981). Similar distribution and excretion patterns were observed after intratracheal injection of nickel chloride (1.27 μg/rat Ni) to male Sprague-Dawley rats (Carvalho & Ziemer, 1982).

Pulmonary clearance and excretion of nickel following intratracheal instillation of nickel sulfate at doses of 17, 190 or 1800 nmol [1, 11 or 106 μg] Ni per rat to

Fischer 344 rats appeared to depend on the dose. At periods up to four days after instillation, lungs, trachea, larynx, kidney and urinary bladder contained the highest concentrations of nickel. The half-time for urinary excretion (the predominant route of excretion) varied from 23 h for the lowest dose to 4.6 h for the highest. Faecal excretion accounted for 30% (17- and 190-nmol doses) and 13% (1800-nmol) of the dose. The long-term half-time of nickel clearance from the lung varied from 21 h at the highest dose to 36 h at the lowest dose (Medinsky *et al.*, 1987).

In male Sprague-Dawley rats exposed to nickel chloride aerosols (90 μg/m³ Ni; 0.7-0.9-μm particles) for 2 h per day for 14 days, the nickel burden in the lung reached a steady level after five days. The maximal clearance velocity was calculated to be 34.6 ng/g.h. These data support the hypothesis of a saturable clearance mechanism for 'soluble nickel' in the lung (Menzel *et al.*, 1987).

After intratracheal administration of 'nickel carbonate' (0.05 mg/mouse Ni) to female Swiss albino mice, most of the dose was eliminated in the urine in about 12 days (Furst & Al-Mahrouq, 1981). [The Working Group noted that the compound tested was most probably basic nickel carbonate.]

After a single intravenous injection of 10 μg nickel as ^{63}Ni-nickel chloride per mouse (albino or brown mice [strains not specified], including pregnant mice), whole-body autoradiography at 30 min showed that nickel persisted in the blood, kidney, urinary bladder, lung, eye and hair follicles; at three weeks, nickel persisted in the lung, central nervous system, kidneys, hair follicles and skin (Bergman *et al.*, 1980). In C57Bl mice, nickel was also localized in the epithelium of the forestomach; in the kidney, it was present in the cortex at sites that probably corresponded to the distal convoluted tubules. Nickel was retained much longer in the lung than in other tissues (Oskarsson & Tjälve, 1979a).

A single intravenous injection of 1 mg/kg bw ^{63}Ni-nickel chloride to male Sprague-Dawley rats resulted in rapid urinary excretion of 87% of the dose in the first day after injection and 90% after four days. Faecal excretion was much lower, up to a total of approximately 3% of the dose after four days (Sunderman & Selin, 1968). Lung and spleen were ranked after kidney as nickel-accumulating organs in Sprague-Dawley rats given an intraperitoneal injection of 82 μg/kg bw ^{63}Ni-nickel chloride (Sarkar, 1980).

The kinetics of nickel metabolism in rats and rabbits after a single intravenous injection of ^{63}Ni-nickel chloride followed a two-compartmental mathematical model, with first-order kinetics of nickel elimination from plasma with half-times of 6 and 50 h for rats and 8 and 83 h for rabbits, respectively, for the two compartments (Onkelinx *et al.*, 1973).

Following a single intraperitoneal injection of ^{63}Ni-nickel chloride to BALB/c mice (100 μCi/mouse), nickel was found to remain in the lung much longer than in

any other tissue (Herlant-Peers *et al.*, 1982). Preferential accumulation of nickel in the lung was also observed in Fischer 344 rats following daily subcutaneous injections of 62.5 or 125 μmol [8.1 or 16.3 mg]/kg bw nickel chloride for up to six weeks (Knight *et al.*, 1988). In contrast, multiple intraperitoneal injections of nickel acetate to male Swiss albino mice (0.5, 0.75 or 1.0 mg/mouse; 10, 20 or 30 daily injections each) resulted in preferential accumulation of nickel in the thymus (Feroz *et al.*, 1976).

Daily oral administration of 2.5 mg nickel sulfate per rat [strain unspecified] for 30 days resulted in accumulation of nickel in trachea > nasopharynx > skull > oesophagus > intestine > skin > liver = spleen > stomach > kidney > lung = brain > heart (Jiachen *et al.*, 1986).

Nickel was taken up from the lumen of male Sprague-Dawley rat jejunum *in vitro* at a rate proportional to the concentration of ^{63}Ni-nickel chloride in the perfusate up to 20 μM [1.2 mg] Ni. At higher concentrations (6 and 12 mg Ni), apparent saturation was approached. Nickel was not retained by the mucosa and showed a very low affinity for metallothionein (Foulkes & McMullen, 1986).

Dermal absorption of 2 or 40 μCi ^{63}Ni-nickel chloride was observed in guinea-pigs. After 1 h, nickel had accumulated in highly keratinized areas, the stratum corneum and hair shafts. Following exposure for 4-48 h, nickel also accumulated in basal and suprabasal epidermal cells. After 4 h, nickel appeared in blood and urine (Lloyd, 1980).

It has been demonstrated in several studies that nickel chloride crosses the placenta in mice (Jacobsen *et al.*, 1978; Lu *et al.*, 1979; Olsen & Jonsen, 1979; Lu *et al.*, 1981; Jasim & Tjälve, 1986) and rats (Sunderman *et al.*, 1977; Mas *et al.*, 1986).

(iv) *Other nickel compounds*

In NMRI mice, high levels of nickel were found in the respiratory tract, brain, spinal cord, heart, diaphragm, adrenal cortex, brown fat, kidney and urinary bladder 5 min to 24 h following inhalation of ^{63}Ni- and ^{14}C-nickel carbonyl at 3.05 g/m^3 Ni for 10 min (Oskarsson & Tjälve, 1979b).

After exposure of rats to nickel carbonyl by inhalation, increased levels of nickel were found predominantly in microsomal and supernatant fractions of the lung and in the microsomal fraction of the liver (Sunderman & Sunderman, 1963).

After an intravenous injection of nickel carbonyl as 22 mg/kg bw Ni to Sprague-Dawley rats, most of the subcellular nickel in liver and lung was bound to supernatant fractions, followed by nuclei and debris, mitochondria and microsomes (Sunderman & Selin, 1968).

Twenty-four hours after an intravenous injection of ^{63}Ni-nickel carbonyl (0.9 mg/kg bw Ni) to NMRI mice, nickel was found to be associated with both particulate and soluble cellular constituents of the lung, liver and kidneys. Radioactivity

was detected in the gel chromatograms of cytosols from lung, kidney and blood serum of treated mice in the void volume and salt volume (Oskarsson & Tjälve, 1979c).

Following intravenous injection of 50 µl/kg bw nickel carbonyl (22 µg/kg bw Ni) to Sprague-Dawley rats, over 38% of the dose was exhaled during 6 h after injection and none after that time. Average total urinary excretion of nickel over four days was 31% (23% within the first 12 h), whereas total faecal excretion was 2.4% and biliary excretion was 0.2%. Total average excretion of nickel in four days was 72%. Most of the remaining nickel carbonyl underwent intracellular decomposition and oxidation to nickel[II] and carbon monoxide. Twenty-four hours after the injection, nickel injected as nickel carbonyl was distributed among organs and tissues, with the highest concentration in lung (Sunderman & Selin, 1968; Kasprzak & Sunderman, 1969).

(*b*) *Dissolution and cellular uptake*

(i) *Metallic nickel and nickel alloys*

Slow dissolution and elimination of finely powdered nickel metal from the muscle injection site was observed in rats. In the local rhabdomyosarcomas that developed, nickel was recovered in the nuclear fraction and mitochondria; little or no nickel was found in the microsomes (Heath & Webb, 1967). The nuclear fraction of nickel is preferentially bound to nucleoli (Webb *et al.*, 1972).

Slow dissolution of metallic nickel occurred when nickel metal powder was incubated at 37°C with horse serum or sterile homogenates of rat muscle, liver, heart or kidney prepared in Tyrode solution. The solubilization may have involved oxygen uptake and was faster for a freshly reduced powder than for an older commercial powder; over 97% of the dissolved nickel became bound to diffusible components of the tissue homogenates (mostly histidine, followed by nucleotides, nucleosides and free bases) (Weinzierl & Webb, 1972).

(ii) *Nickel oxides and hydroxides*

The dissolution half-times of six differently prepared samples of nickel oxide and four samples of nickel-copper oxides in water were longer than 11 years. However, in rat serum and renal cytosol, the half-time dropped to about one year for a low-temperature nickel oxide and to 2.7-7.2 years for three nickel-copper oxides, the rest retaining the > 11-year value. Two preparations of nickel oxide obtained at temperatures ≤735°C and all four nickel-copper oxides appeared to be phagocytized by C3H/10T½ cells more actively than the other nickel oxides (Sunderman *et al.*, 1987).

Kasprzak *et al.* (1983) found the half-times for two preparations of nickel hydroxide (air-dried colloidal and crystalline) in an 0.1 M ammonium acetate buffer of

pH 7.4 to be 56 h and 225 h, respectively. Corresponding values in an artificial lung fluid were 360 h and 1870 h, respectively.

(iii) *Nickel sulfides*

The dissolution rate of α-nickel subsulfide depends on the particle size, the presence of oxygen and the dissolving medium (Gilman & Herchen, 1963; Kasprzak & Sunderman, 1977; Dewally & Hildebrand, 1980; Lee *et al.*, 1982).

Both *in vivo* and in cell-free systems *in vitro*, α-nickel subsulfide reacts with oxygen to yield insoluble crystalline β-nickel sulfide and soluble nickel[II] derivatives; β-nickel sulfide also dissolves through oxidation of its sulfur moiety (Kasprzak & Sunderman, 1977; Oskarsson *et al.*, 1979; Dewally & Hildebrand, 1980). It has been suggested that the transformation of nickel subsulfide into β-nickel sulfide under anaerobic conditions in the muscle might be due to reaction with sulfur from sulfhydryl groups in the host organism (Dewally & Hildebrand, 1980).

Particles of crystalline nickel sulfides, α-nickel subsulfide and β-nickel sulfide (<5 μm in diameter, 1-20 μg/ml) were phagocytized by cultured Syrian hamster embryo cells and Chinese hamster CHO cells, while particles of amorphous nickel sulfide were taken up only sparingly by the cells. Pretreatment of Syrian hamster embryo cells with benzo[*a*]pyrene enhanced the uptake of nickel subsulfide. The half-life of the engulfed particles was about 40 h in Syrian hamster cells; they disappeared from the cells through solubilization, and solubilized nickel was detected in the nuclear fraction (Costa & Mollenhauer, 1980a,b; Costa *et al.*, 1981a).

α-Nickel subsulfide and β-nickel sulfide were also incorporated into human embryonic L132 pulmonary cells in culture. β-Nickel sulfide was present within large intracellular vesicles; nickel subsulfide was generally bound to the membranes of intracellular vesicles, to lysosomal structures and to the outer cell membrane (Hildebrand *et al.*, 1985, 1986).

The soluble nickel derived from nickel subsulfide and β-nickel sulfide intracellularly undergoes subcellular distribution that differs from that following entry of nickel from outside the cells (Harnett *et al.*, 1982; Sen & Costa, 1986a). Treatment of cultured Chinese hamster CHO cells with β-nickel sulfide (10 μg/ml, three-day incubation) resulted in binding of nickel to DNA and RNA at a level 300-2000 times higher and to protein at a level 15 times higher than after similar treatment with nickel chloride (Harnett *et al.*, 1982). Cellular uptake of β-nickel sulfide facilitates a specific interaction of nickel with the heterochromatic long arm of the X chromosome of Chinese hamster CHO cells (Sen & Costa, 1986a). Lee *et al.* (1982) found that soluble nickel derived from nickel subsulfide forms an exceptionally stable ternary protein-nickel-DNA complex *in vitro* in the presence of DNA and rat liver microsomes.

(iv) *Nickel salts*

Soluble nickel retained in the tissues of mice becomes bound to particulate and soluble cellular constituents, the distribution depending on the tissue. In lung and liver of NMRI mice, nickel was bound predominantly to a high-molecular-weight protein; in the kidney, it was bound mainly to low-molecular-weight ultrafiltrable ligands. No nickel was bound to metallothionein or superoxide dismutase (Oskarsson & Tjälve, 1979c).

Several nickel-binding proteins were found in lung and liver cytosol of BALB/c mice that were different after incorporation *in vivo* and *in vitro*. The composition and structures of these proteins were not identified (Herlant-Peers *et al.*, 1982).

Intracellular nickel concentrations in the lungs of strain A mice given intraperitoneal injections of nickel acetate were highest in the microsomes, followed by mitochondria, cytosol and nuclei (Kasprzak, 1987).

In blood serum, nickel was sequestered mainly by albumin, which had a high binding capacity for this metal in most species tested, except for dogs and pigs (Callan & Sunderman, 1973). Nickel in human serum is chelated by histidine, serum albumin or both in a ternary complex, although a small fraction is bound to a glycoprotein (Sarkar, 1980; Glennon & Sarkar, 1982).

Less nickel chloride was taken up by Chinese hamster CHO cells than insoluble nickel sulfides; moreover, nickel incorporated from nickel chloride had a much higher affinity for cellular proteins than for DNA or RNA (Harnett *et al.*, 1982). A greater effect on the heterochromatic long arm of the X chromosome was observed when Chinese hamster CHO cells were exposed to nickel-albumin complexes encapsulated in liposomes than to nickel chloride alone (Sen & Costa, 1986a).

Cellular binding and uptake of nickel depend on the hydro- and lipophilic properties of the nickel complexes to which the cells are exposed. Nickel-complexing ligands, L-histidine, human serum albumin, D-penicillamine and ethylenediaminetetraacetic acid, which form hydrophilic nickel complexes, inhibited the uptake of nickel by rabbit alveolar macrophages, human B-lymphoblasts and human erythrocytes. The same ligands also sequestered nickel from nickel-preloaded cells. Diethyldithiocarbamate, however, which forms a lipophilic nickel complex, enhanced the cellular uptake of nickel and prevented its removal from nickel-preloaded cells. It also induced transfer of nickel in a cell lysate from the cytosol to the residual pellet (Nieboer *et al.*, 1984b). Sodium pyridinethione, which forms a lipophilic nickel complex, behaved similarly (Jasim & Tjälve, 1986).

Nickel applied to rat liver and kidney nuclei as nickel chloride bound in a dose-related manner to the chromatin and as to polynucleosomes and to the DNA molecule. In the nuclear chromatin, nickel was associated with both the DNA and histone and non-histone proteins; a ternary nickel-DNA-protein complex more

stable than binary nickel-DNA complexes was identified (Ciccarelli & Wetterhahn, 1985).

Calf thymus DNA appeared to have more than two types of binding site for nickel; DNA phosphate moieties were identified as having the highest affinity for nickel (Kasprzak *et al.*, 1986).

(v) *Other nickel compounds*

'Nickel carbonate' particles were actively phagocytized by human embryonal lung epithelial cells L132 in culture and showed an increased affinity for cytoplasmic and cell membranes (Hildebrand *et al.*, 1986). [The Working Group noted that the compound tested was most probably basic nickel carbonate.]

Following an intraperitoneal injection of 'nickel carbonate' to male Sprague-Dawley rats, nickel was found to be associated with liver and kidney nuclear DNA as early as 3 h after injection, with a further increase by 20 h. The nickel concentration in kidney DNA was five to six times higher than that in liver. Significant differences were found in the distribution of nickel between nucleic acids and associated proteins in DNA samples extracted from kidney and liver (Ciccarelli & Wetterhahn, 1984a,b). [The Working Group noted that the compound tested was most probably basic nickel carbonate.]

Sunderman *et al.* (1984b) determined dissolution half-times in rat serum and renal cytosol and phagocytic indices in peritoneal macrophages *in vitro* of various water-insoluble nickel derivatives, including nickel selenide, nickel subselenide, nickel telluride, nickel sulfarsenide, nickel arsenide, nickel arsenide tetragonal, nickel arsenide hexagonal, nickel antimonide, nickel ferrosulfide matte, a ferronickel alloy ($NiFe_{1-6}$) and nickel titanate. No correlation was found between those two parameters and the carcinogenic activity of the tested compounds in the muscle of Fischer 344 rats.

(c) *Interactions*

Parenteral administration of soluble nickel salts induced changes in the tissue distribution of other metal ions (Whanger, 1973; Nielsen, 1980; Chmielnicka *et al.*, 1982; Nieboer *et al.*, 1984b; Nielsen *et al.*, 1984).

Several physiological divalent cations appeared to affect nickel metabolism. Thus, manganese decreased the proportion of ultrafiltrable nickel constituents of muscle homogenates; the gross muscle uptake and excretion of nickel were not affected. Metallic manganese dust also inhibited the dissolution rate of nickel subsulfide in rat serum, serum ultrafiltrate and water (Sunderman *et al.*, 1976). Manganese dust reduced the phagocytosis of nickel subsulfide particles by Syrian hamster embryo cells *in vitro* (Costa *et al.*, 1981a). Magnesium decreased the uptake of nickel by pulmonary nuclei and cytosol of strain A mice and decreased nickel uptake by

lung, kidney and liver of Fischer 344 rats (Kasprzak *et al.*, 1987). Both manganese and magnesium strongly antagonized the binding of nickel to the phosphate groups of calf thymus DNA *in vitro*, while copper, which did not inhibit nickel carcinogenesis, was a much weaker antagonist (Kasprzak *et al.*, 1986).

Nickel that accumulated in mouse tissues following administration of nickel carbonyl *in vivo* could be displaced from those tissues by treatment *in vitro* with other cations, including H^+, in proportion to their valence; Mg^{2+} and La^{3+} were the most effective (Oskarsson & Tjälve, 1979b).

Certain nickel[II]-peptide complexes in aqueous solution were found to react with ambient oxygen by a facile autocatalytic process in which nickel[III] intermediates played a major role. Such reactions may lead to degradation, e.g., decarboxylation, of the organic ligand (Bossu *et al.*, 1978). Nickel[III] was also identified in a nickel[II]-glycyl-glycyl-*n*-histidine complex, indicating possible redox effects of the nickel[III]/nickel[II] redox couple on that protein (Nieboer *et al.*, 1986).

(*d*) *Toxic effects*

The toxicity of nickel and its inorganic compounds has been reviewed (US Environmental Protection Agency, 1986; Fairhurst & Illing, 1987; World Health Organization, 1990), and the chemical basis of the biological reactivity of nickel has been discussed (Ciccarelli & Wetterhahn, 1984a; Nieboer *et al.*, 1984b,c).

(i) *Metallic nickel and nickel alloys*

The lungs of male rabbits exposed by inhalation to 1 mg/m^3 nickel metal dust (< 40 μm particles) for 6 h per day on five days per week for three and six months showed two- to three-fold increases in the volume density of alveolar type II cells. The six-month exposure caused focal pneumonia (Johansson *et al.*, 1981; Camner *et al.*, 1984).

Similar changes, resembling alveolar proteinosis, were observed in rabbits after exposure to nickel metal dust by inhalation for four weeks (Camner *et al.*, 1978). After three or six months of exposure at 1 mg/m^3, phagocytic activity *in vitro* was increased upon challenge by *Escherichia coli* (Johansson *et al.*, 1980).

A single intramuscular injection of 20 mg nickel metal dust to male WAG rats resulted in long-lasting suppression of natural killer cell activity in peripheral blood mononuclear cells. Between eight and 18 weeks after the nickel injection, the activity decreased to 50-60% of that in the control rats (Judde *et al.*, 1987).

(ii) *Nickel oxides*

Exposure of female Wistar rats by inhalation to nickel monoxide aerosols (generated at 550 °C from nickel acetate) at concentrations of 200, 400 and 800 μg/m^3 for 24 h per day for 120 days resulted in a significant, dose-related reduction in growth

rate, decreased kidney and liver weights and erythrocyte count, decreased activity of serum alkaline phosphatase, increased wet lung weight and leukocyte count and increased mean erythrocyte cell volume (Weischer *et al.*, 1980a,b).

Male Wistar rats exposed continuously to nickel monoxide (generated at 550°C from nickel acetate) aerosols at 50 μg/m³ (median particle diameter, 0.35 μm) for 15 weeks showed no significant difference in the overall ability of the lungs to clear ferrous oxide up to day 7. After that time, lung clearance in nickel oxide-exposed rats decreased significantly. The half life of ferrous oxide clearance after day 6 was 58 days for control rats and 520 days for nickel oxide-exposed rats; in excised lungs, the values were 56 and 74 days, respectively (Oberdoerster & Hochrainer, 1980).

An increase in lung weight (six-fold) and alveolar proteinosis were observed in male Wistar rats that died during life-time exposure to an aerosol of nickel monoxide (produced by pyrolysis of nickel acetate [probably at 550°C] [particle size unspecified]) at 60 or 200 μg/m³, 23 h per day, seven days per week. With longer exposures, marked accumulation of macrophages and focal septal fibrosis were also observed (Takenaka *et al.*, 1985).

No significant histopathological change was found in male Wistar rats exposed to green nickel oxide (0.6 μm particles) for up to 12 months at 0.3 or 1.2 mg/m³, 7 h per day on five days per week (Tanaka *et al.*, 1988).

No mortality was observed following exposure by inhalation of Fischer 344/N rats and B6C3F$_1$ mice to nickel monoxide (formed at 1350°C; 3 μm particles) at 0.9-24 mg/m³ Ni for 6 h/day on five days per week for 12 days. Lung inflammation and hyperplasia of alveolar macrophages occurred primarily at the highest exposure concentration in both species; generally, the lung lesions in mice were less severe than those in rats. Atrophy of the olfactory epithelium was seen only in two rats at the highest dose, while atrophy of the thymus and hyperplasia of the lymph nodes were seen in both rats and mice exposed to the highest concentrations (Dunnick *et al.*, 1988).

In Syrian golden hamsters, life-time inhalation of 53 mg/m³ nickel monoxide ([unspecified] 0.3 μm particles) for 7 h per day resulted in emphysema in animals that died early in the experiment. Other lung effects included interstitial pneumonitis and diffuse granulomatous pneumonia, fibrosis of alveolar septa, bronchiolar (basal-cell) hyperplasia, bronchiolization of alveolar epithelium, squamous metaplasia and emphysema and/or atelectasia of various degrees (Wehner *et al.*, 1975).

The median lethal concentration for rat macrophages exposed *in vitro* to green nickel monoxide exceeded 12 μmol (708 μg)/ml Ni. The LC_{50} for canine macrophages was 3.9 μmol (230 μg)/ml Ni as nickel monoxide for 20 h. Nickel monoxide was far less toxic to macrophages than nickel sulfate, nickel chloride or nickel

subsulfide (Benson *et al.*, 1986a). The toxicity of six different preparations of nickel monoxide calcined at temperatures of < 650-1045 °C and four mixed nickel-copper oxides was tested *in vitro* on alveolar macrophages of beagle dogs, Fischer 344 rats and $B6C3F_1$ mice. Nickel oxides were less toxic to the macrophages than were the nickel-copper oxides; the toxicity of the nickel-copper oxides increased with increasing copper content. Generally, dog macrophages were more sensitive to the oxides than mouse and rat macrophages (Benson *et al.*, 1988a).

The ability of the same oxides to stimulate erythropoiesis in Fischer 344 rats correlated well with their cell transforming ability in Syrian hamster embryo cells (see also genetic and related effects; Sunderman *et al.*, 1987).

(iii) *Nickel sulfides*

The LD_{50} after a single instillation in $B6C3F_1$ mice of nickel subsulfide (particle size, < 2 μm) in a normal saline suspension was 4 mg/kg bw (Fisher *et al.*, 1986).

Acute toxic effects of nickel subsulfide (1.8 μm particles) administered intratracheally to male BALB/c mice (12 μg/mouse) included pulmonary haemorrhaging, most evident three days after exposure. The number of polymorphonuclear cells in the pulmonary lavage fluid was increased, whereas the number of macrophages tended to decrease below the control values later (20 h to seven days) after the exposure (Finch *et al.*, 1987).

Alveolitis was observed in Fischer 344 rats following intratracheal instillation of nickel subsulfide as a saline/gelatin suspension (3.2-320 μg/kg bw). The effects closely resembled those of nickel chloride and nickel sulfate at comparable doses of nickel. Pulmonary lesions also included type II cell hyperplasia with epithelialization of alveoli and, in some animals, fibroplasia of the pulmonary interstitium (Benson *et al.*, 1986b).

Chronic active inflammation, fibrosis and alveolar macrophage hyperplasia were observed in Fischer 344 rats and $B6C3F_1$ mice exposed by inhalation to nickel subsulfide (low-temperature form) for 13 weeks (6 h per day, five days per week; 0.11-1.8 mg/m³ Ni). The toxicity of nickel subsulfide to the lung resembled that of nickel sulfate hexahydrate, and both were more toxic than nickel oxide. Rats were more sensitive than mice (Dunnick *et al.*, 1989).

Administration of nickel subsulfide to female rats as a single intrarenal injection caused pronounced erythrocytosis (Jasmin & Riopelle, 1976; Oskarsson *et al.*, 1981). A single intrarenal injection of nickel subsulfide to male rats also caused an increase in renal haem oxygenase activity; no correlation between the induction of haem oxygenase and erythrocytosis was observed (Sunderman *et al.*, 1983a). Administration of nickel sulfide [probably amorphous] in glycerine or saline into each pole of the kidney of female rats did not induce renal erythropoietic activity (Jasmin & Riopelle, 1976).

Under comparable exposure *in vitro*, beagle dog alveolar macrophages were more sensitive to the toxicity of nickel subsulfide than were those of Fischer 344 rats. Nickel subsulfide appeared to be much more toxic to the macrophages of both species than nickel chloride, nickel sulfate or nickel monoxide (Benson *et al.*, 1986a).

Nickel subsulfide incubated with calf thymus histones in the presence of molecular oxygen caused random polymerization of those proteins; this effect was not produced by soluble nickel acetate (Kasprzak & Bare, 1989).

(iv) *Nickel salts*

The oral LD_{50} of nickel acetate was 350 mg/kg bw in rats and 420 mg/kg bw in mice; the intraperitoneal LD_{50} was 23 mg/kg bw in rats (National Research Council, 1975). The LD_{50} of nickel acetate in ICR mice after an intraperitoneal injection was 97 mg/kg bw in females and 89 mg/kg bw in males at days 3 and 5 for three-week-old animals and 39-54 mg/kg bw in nine- or 14-week-old animals of either sex (Hogan, 1985). With nickel chloride, intraperitoneal LD_{50} values of 6-9.3 mg/kg bw Ni were reported for female Wistar rats (Mas *et al.*, 1985), 11 mg/kg bw rats and 48 mg/kg bw for mice (National Research Council, 1975).

Exposure of $B6C3F_1$ mice and Fischer 344/N rats to nickel sulfate hexahydrate by inhalation for 6 h per day for 12 days (five days per week plus two consecutive days; 0.8-13 mg/m^3 Ni; 2 μm particles) caused death of all mice at concentrations of $\geq$1.6 mg/m^3 and of some rats at concentrations of 13 mg/m^3. Lesions of the lung and nasal cavity were observed in both mice and rats after exposure to 0.8 mg/m^3 nickel or more; these included necrotizing pneumonia, chronic inflammation and degeneration of the bronchiolar epithelium, atrophy of the olfactory epithelium, and hyperplasia of the bronchial and mediastinal lymph nodes (Benson *et al.*, 1988b; Dunnick *et al.*, 1988).

A single intratracheal instillation of nickel chloride hexahydrate or nickel sulfate hexahydrate to Fischer 344/Cr1 rats (0.01, 0.1 or 1.0 μmol [0.59, 5.9 or 59 μg Ni/rat) caused alveolitis and affected the activities of several enzymes measured in the pulmonary lavage fluid (Benson *et al.*, 1985, 1986b).

Rabbits were exposed to nickel chloride (0.2-0.3 mg/m^3 Ni) for 6 h per day on five days per week for one to eight months. Nodular accumulation of macrophages was seen in lung tissue, and the volume density of alveolar type II cells was elevated. The phagocytic activity of macrophages was normal after one month of exposure but was decreased after three months (Camner *et al.*, 1984; Lundborg & Camner, 1984; Camner *et al.*, 1985).

Exposure of Syrian golden hamsters to a nickel chloride aerosol (100-275 μg/m^3 Ni; <2-μm particles) for 2 h per day for one or two days resulted in a dose-related decrease in the ciliary activity of the tracheal epithelium and in mucosal degeneration (Adalis *et al.*, 1978).

A single intramuscular injection of nickel chloride (18.3 mg/kg bw) to male CBA/J mice caused significant involution of the thymus within two days. Significant reduction in the mitogen-stimulated responses of B and T lymphocytes *in vitro* as well as significant suppression of the primary antibody response (T-cell-dependent) to sheep red blood cells were observed after the treatment. Natural killer cell activity was also suppressed. The immunosuppressive effects of nickel chloride lasted for a few days. The activity of peritoneal macrophages was not affected (Smialowicz *et al.*, 1984, 1985).

Following a single intramuscular injection of 10-20 mg/kg bw nickel chloride into Fischer 344 rats, the activity of natural killer cells was transiently suppressed for three days. In contrast to mice, rats showed no significant difference in the lymphoproliferative responses of splenocytes to B and T mitogens from those of controls (Smialowicz *et al.*, 1987).

Intramuscular injection of nickel chloride (20 mg/kg bw Ni) to Fischer 344 rats 4 h before death inhibited thymidine uptake into kidney DNA (Hui & Sunderman, 1980). An immediate, significant decrease, followed by a transient sharp increase of thymidine incorporation into pulmonary DNA was observed in strain A mice following intraperitoneal administration of nickel acetate (Kasprzak & Poirier, 1985).

After 90 daily intraperitoneal injections of nickel sulfate (3 mg/kg bw Ni) to male albino rats, focal necrosis of the proximal convoluted tubules in the kidneys and marked cellularity around periportal areas and necrotic areas in the liver were observed. Bile-duct proliferation and Kupffer-cell hyperplasia were also evident, and degenerative changes were observed in a few seminiferous tubules and in the inner wall of the myocardium (Mathur *et al.*, 1977a).

Subcutaneous injection of up to 0.75 mmol [98 mg]/kg bw nickel chloride to male Fischer 344 rats increased lipid peroxidation in the liver, kidney and lung in a dose-related manner (Sunderman *et al.*, 1985b).

Renal, hepatic, pulmonary and brain haem oxygenase activity was induced after subcutaneous injection of 15 mg/kg bw nickel chloride to male Fischer 344 rats. Induction of haem oxygenase was also observed in the kidneys of male BL6 mice, male Syrian golden hamsters and male guinea-pigs killed 17 h after subcutaneous injection of 0.25 mmol [32 mg]/kg bw nickel chloride (Sunderman *et al.*, 1983a).

The skin of male albino rats was painted once daily for up to 30 days with 0.25 ml nickel sulfate hexahydrate solution in normal saline (40, 60 and 100 mg/kg bw Ni). The 30-day painting caused atrophy in some areas and acanthosis in other areas of the epidermis, disorder in the arrangement of epidermal cells and hyperkeratinization. Liver damage, including focal necrosis, was seen in histological studies (Mathur *et al.*, 1977b).

The toxicity of nickel sulfate and nickel chloride to alveolar macrophages from beagle dogs and Fischer 344 rats *in vitro* was intermediate to that of nickel subsulfide and nickel monoxide (median lethal concentrations, 0.30-0.36 μmol [17.7-21.2 μg] and 3.1-3.6 μmol [183-212 μg]/ml Ni for dog and rat macrophages, respectively) (Benson *et al.*, 1986a). Macrophages lavaged from rabbit lungs and incubated for two days with 3-24 μg/ml Ni as nickel chloride showed a decrease of up to 50% in lysozyme activity with increasing concentrations of nickel (Lundborg *et al.*, 1987).

Although nickel salts inhibit the proliferation of normal mammalian cells in culture, nickel sulfate hexahydrate increased proliferation of some lymphoblastoid cell lines carrying the Epstein-Barr virus (Wu *et al.*, 1986).

Exposure of Syrian hamster embryo cells to nickel chloride or nickel sulfate at a concentration of 10 μmol [600 μg]/l Ni or more enhanced nucleoside excretion (Uziel *et al.*, 1986).

Nickel chloride inhibited the transcription of calf thymus DNA and phage T4 DNA with *Escherichia coli* RNA polymerase in a concentration-dependent manner (0.01-10 mM [0.6-600 mg] Ni). It also stimulated RNA chain initiation at very low concentrations (maximal at 0.6 mg), followed by a progressive decrease in initiation at concentrations that significantly inhibited overall transcription (Niyogi *et al.*, 1981).

(v) *Other nickel compounds*

Animals exposed to nickel carbonyl by inhalation developed pulmonary oedema within 1 h. LC_{50} values (30-min exposure) reported include 67 mg/m^3 for mice, 240 mg/m^3 for rats and 190 mg/m^3 for cats (National Research Council, 1975). Even after administration by other routes, the lung is the main target organ (Hackett & Sunderman, 1969); the LD_{50} for rats was 65 mg/kg, 61 mg/kg and 38 mg/kg after intravenous, subcutaneous and intraperitoneal administration, respectively (National Research Council, 1975).

Male Wistar rats exposed by inhalation to 0.03-0.06 mg/l nickel carbonyl for 90 min three times a week for 52 weeks developed extensive inflammatory lesions in the lung, contiguous pericarditis and suppurative lesions of the thoracic walls. Squamous-cell metaplasia was present in bronchiectatic walls of several rats (Sunderman *et al.*, 1957).

Exposure of female Fischer 344 rats by inhalation to 1.2-6.4 μmol [0.2-1.1 mg]/l nickel carbonyl for 15 min caused acute hyperglycaemia (Horak *et al.*, 1978). Urinary excretion of proteins and amino acids indicated nephrotoxicity (Horak & Sunderman, 1980).

After exposure of rats to 0.6 mg/l nickel carbonyl by inhalation, RNA derived from the lung showed alterations in the phase transition curve, indicating disruption of hydrogen bonds (Sunderman, 1963). Nickel carbonyl administered

intravenously at an LD_{50} dose of 20 mg/kg bw nickel to Sprague-Dawley rats inhibited cortisone-induced hepatic tryptophan pyrrolase (Sunderman, 1967), orotic acid incorporation into liver RNA *in vivo* and *in vitro* (Beach & Sunderman, 1969, 1970) and incorporation of leucine into liver and lung protein (Witschi, 1972). Intravenous administration of nickel carbonyl to Fischer 344 rats (20 mg/kg bw nickel) caused a significant decrease in thymidine incorporation into liver and kidney DNA 4 h later (Hui & Sunderman, 1980).

The toxicity of 'nickel carbonate' to human embryo pulmonary epithelium L132 cells in culture did not differ significantly from that of nickel chloride at the same 25-150 μM concentration range applied (Hildebrand *et al.*, 1986). [The Working Group noted that the compound tested was most probably basic nickel carbonate.]

A highly significant correlation was found between carcinogenic potential and the incidence of erythrocytosis for various water-insoluble nickel compounds, including nickel selenide, nickel subselenide, nickel telluride, nickel sulfarsenide, nickel arsenide, nickel arsenide tetragonal, nickel arsenide hexagonal, nickel antimonide, nickel ferrosulfide matte, a ferronickel alloy ($NiFe_{1-6}$) and nickel titanate (Sunderman *et al.*, 1984b).

Dusts of nickel-converter mattes (58% nickel sulfide, 11% metallic nickel, 2% nickel monoxide, 1% copper, 0.5% cobalt, 0.2% soluble nickel salts), a nickel concentrate (67% total nickel, 57% nickel sulfide) and two nickel-copper mattes (27-33% nickel sulfides, ~3% metallic nickel, 23-36% copper) were administered to white rats and mice by inhalation or by intragastric, intratracheal or intraperitoneal routes and onto the skin. The intratracheal LD_{50} was 200-210 mg/kg bw for the mattes and 220 mg/kg for the nickel concentrate. The intraperitoneal LD_{50} varied from 940 mg/kg bw for the nickel concentrate to 1000 mg/kg bw for the nickel-copper mattes and 1100 mg/kg bw for the nickel matte. Mice and rats were almost equally sensitive. Chronic exposure of rats and mice by inhalation to the same dusts caused bronchitis, perivasculitis, bronchopneumonia and fibrosis. Haemorrhagic foci and atrophy were observed in the kidneys (Saknyn *et al.*, 1976).

(*e*) *Effects on reproduction and prenatal toxicity*

The embryotoxicity and genotoxicity of nickel, both directly to the mammalian embryo and indirectly through maternal injury, have been reviewed (Léonard & Jacquet, 1984).

(i) *Metallic nickel and nickel alloys*

Treatment of chick embryo myoblasts with 20-40 μg nickel powder per litre of culture fluid prevented normal differentiation of cells, with only a few mitoses seen after five days' incubation. Reduction of cell division was coupled with cell

degeneration, resulting in small colony size. At concentrations of 80 µg/l nickel, extensive degeneration of the cultures and complete suppression of mitosis occurred within five days (Daniel *et al.*, 1974).

(ii) *Nickel sulfides*

Nickel subsulfide (80 mg/kg bw Ni) administered intramuscularly to Fischer rats on day 6 of gestation reduced the mean number of live pups per dam. No anomaly was found, and no evidence of maternal toxicity was reported (Sunderman *et al.*, 1978a). In another study, intrarenal injection of nickel subsulfide (30 mg/kg bw Ni) to female rats prior to breeding produced intense erythrocytosis in pregnant dams but not in the pups, which had reduced blood haematocrits at two weeks (Sunderman *et al.*, 1983b).

Both rats and mice administered 5 or 10 mg/m^3 nickel subsulfide aerosols by inhalation for 12 days developed degeneration of testicular germinal epithelium (Benson *et al.*, 1987).

(iii) *Nickel salts*

Studies on the teratogenic effects of nickel chloride in chick embryos have produced conflicting results, perhaps due to differences in dose and route of administration. Cardiac anomalies (Gilani, 1982), exencephaly and distorted skeletal development (Gilani & Marano, 1980) have been reported, whereas some authors found no nickel-induced anomaly (Ridgway & Karnofsky, 1952; Anwer & Mehrotra, 1986).

Embryo cultures from BALB/c mice were used to determine the mechanism of preimplantation loss of embryos derived from matings three and four weeks after treatment of males with 40 or 56 mg/kg bw nickel nitrate. Treated and control animals were allowed to mate with superovulated females and the number of cleaved eggs and the development of embryos to blastocysts and implantations were counted. Neither the fertilizing capacity of spermatozoa nor the development of cultured embryos was influenced by a dose of 40 mg/kg bw. A dose of 56 mg/kg bw significantly reduced the fertilization rate but did not affect the development of two-cell embryos. The results suggest that preimplantation loss after exposure to nickel is due to toxic effects on spermatids and spermatogonia rather than to zygotic death (Jacquet & Mayence, 1982).

Following daily intragastric administration of 25 mg/kg bw nickel sulfate to male white rats over a period of 120 days, severe lesions in germ-cell development in the testis were observed (Waltscheva *et al.*, 1972). Rats administered nickel sulfate by inhalation for 12 days developed testicular degeneration (Benson *et al.*, 1988b).

Groups of three to five male albino rats received subcutaneous injections of 0.04 mmol [6.2 mg]/kg bw nickel sulfate either as a single dose or as daily doses for

up to 30 days. Treatment interfered to some degree with spermatogenesis, but this was temporary, and the testes ultimately recovered (Hoey, 1966).

Preimplantation embryos from NMRI mice (two- and four- to eight-cell stages) were cultured with nickel chloride hexahydrate; 10 μM (2.5 mg) adversely affected the development of day 2 embryos (two-cell stage), whereas 300 μM (71.3 mg) were required to affect day 3 embryos (eight-cell stage) (Storeng & Jonsen, 1980). In order to compare the effects of nickel chloride hexahydrate on mouse embryos treated *in vivo* by intraperitoneal injection during the preimplantation period, a single injection of 20 mg/kg bw nickel chloride was given to groups of female mice on day 1, 2, 3, 4, 5 or 6 of gestation. On day 19 of gestation, the implantation frequency in females treated on day 1 was much lower than that of controls. The litters of the control group were larger, and significantly so, among mice treated on days 1, 3 and 5 of gestation; the body weight of fetuses was also decreased on day 19. Nickel chloride may thus adversely affect mouse embryos during the passage through the oviduct, with subsequent effects after implantation. Data on maternal effects were not presented (Storeng & Jonsen, 1981).

Long-Evans rats born in a laboratory especially designed to avoid environmental contamination from trace metals were administered nickel [salt unspecified] at 5 mg/l in the drinking-water in five pairs. About one-third of the offspring in the first generation were runts, and one maternal death occurred. In the second generation, there were 10% young deaths with only 5% runts and, in the third generation, 21% young deaths with 6% runts. Thus, the size of the litters decreased somewhat with each generation and, with some failures in breeding, the number of rats was reduced (Schroeder & Mitchener, 1971). A subsequent study, reported in an abstract, found similar effects on reproduction through two generations of rats following administration of 500 mg/l nickel chloride in drinking-water. There was no decrease in maternal weight gain or other maternal effect (Kimmel *et al.*, 1986).

Nickel chloride was administered in the drinking-water to female rats at a concentration of 0.1 or 0.01 mg/l Ni for seven months and then during pregnancy. Embryonic mortality was 57% among nine rats exposed to the higher concentration, compared to 34% among eight controls. At the lower concentration no such difference was observed (Nadeenko *et al.*, 1979).

Nickel chloride (1.2-6.9 mg/kg bw Ni) was administered intraperitoneally to pregnant ICR mice on single days between days 7-11 of gestation. Increased resorption, decreased fetal weight, delayed skeletal ossification and a high incidence of malformations were observed in a dose-related fashion on gestation day 18. The malformations consisted of acephaly, exencephaly, cerebral hernia, open eyelids, cleft palate, micromelia, ankylosis of the extremities, club foot and other skeletal

abnormalities. Five of 27, 6/25 and 7/24 dams receiving 4.6 mg/kg bw or more died within 72 h after injection on days 9, 10 and 11 (Lu *et al.*, 1979).

Fischer rats were administered nickel chloride (16 mg/kg bw Ni) intramuscularly on day 8 of gestation. The body weight of fetuses on day 20 of gestation and of weanlings four to eight weeks after birth were reduced. No congenital anomaly was found in fetuses from nickel-treated dams, or in rats that received ten intramuscular injections of 2 mg/kg bw Ni as nickel chloride twice daily from day 6 to day 10 of gestation (Sunderman *et al.*, 1978a).

Groups of pregnant Wistar rats were given nickel chloride (1, 2 or 4 mg/kg bw Ni) by intraperitoneal injection on days 8, 12 and 16 of pregnancy and were sacrificed on day 20. More malformations occurred when nickel was administered during organogenesis than after, and their occurrence was maximal at dose levels that were toxic to dams. The abnormalities included hydrocephalus, haemorrhage, hydronephrosis, skeletal retardation and one heart defect (Mas *et al.*, 1985).

(iv) *Other nickel compounds*

Nickel carbonyl (11 mg/kg bw Ni) was injected intravenously into pregnant Fischer rats on day 7 of gestation. On day 20, fetal mortality was increased, the body weight of live pups was decreased and there was a 16% incidence of fetal malformations, including anophthalmia, microphthalmia, cystic lungs and hydronephrosis. No information was given regarding maternal toxicity (Sunderman *et al.*, 1983b).

Fischer rats were exposed on day 7 or 8 of gestation by inhalation to nickel carbonyl at concentrations of 80, 160 or 360 mg/m^3 for 15 min. Ophthalmic anomalies (anophthalmia and microphthalmia) were observed in 86/511 fetuses from 62 pregnancies; they were most prevalent at the highest dose level and were not observed when the compound was given on day 9 of gestation (Sunderman *et al.*, 1979b). In another experiment, pregnant rats exposed to 60 or 120 mg/m^3 nickel carbonyl by inhalation for 15 min on day 8 of gestation also had a high incidence of ocular anomalies. Maternal toxicity was not reported (Sunderman *et al.*, 1978b).

Groups of pregnant hamsters were administered 60 mg/m^3 nickel carbonyl by inhalation for 15 min on days 4, 5, 6, 7 or 8 of gestation. Dams were sacrificed on day 15 and the fetuses examined for malformation. Exposure on days 4 and 5 of gestation resulted in malformations in about 5.5% of the progeny, which included cystic lung, exencephaly, fused rib, anophthalmia, cleft palate and haemorrhage into the serous cavities. Nine of 14 dams lived until day 16 of gestation. Haemorrhages were not observed in controls. Among the fetuses of dams exposed to nickel carbonyl on day 6 or 7 of gestation, one fetus had fused ribs and two had hydronephrosis. For pregnancies allowed to reach full-term, there was no significant difference on the day of delivery between pups from nickel carbonyl-exposed litters and controls. Neonatal mortality was increased (Sunderman *et al.*, 1980).

(f) *Genetic and related effects*

Many reviews of the genetic effects of nickel compounds have been published (Heck & Costa, 1982; Christie & Costa, 1984; Costa & Heck, 1984; Hansen & Stern, 1984; Reith & Brøgger, 1984; Costa & Heck, 1986; Fairhurst & Illing, 1987; Sunderman, 1989).

The genotoxic effects of different nickel compounds are divided into five categories: (i) those for metallic nickel; (ii) those for nickel oxides and hydroxides; (iii) those for crystalline nickel sulfide, crystalline nickel subsulfide and amorphous nickel sulfide; (iv) those for nickel chloride, nickel sulfate, nickel acetate and nickel nitrate; and (v) those for nickel carbonate, nickelocene, nickel potassium cyanide and nickel subselenide. The studies on these compounds are summarized in Appendix 1 to this volume.

(i) *Metallic nickel*

Nickel powder was reported not to induce chromosomal aberrations in cultured human peripheral lymphocytes [details not given] (Paton & Allison, 1972).

Nickel powder ground to a mean particle size of 4-5 μm at concentrations of 5, 10 and 20 μg/ml caused a dose-dependent increase in morphological transformation of Syrian hamster embryo cells (Costa *et al.*, 1981b). At 20 μg/ml, nickel powder produced a 3% incidence of transformation, while crystalline nickel subsulfide and crystalline nickel sulfide (at 10-20 μg/ml) produced a 10-13% incidence of transformation and 5 and 10 μg/ml of amorphous nickel sulfide induced none. Nickel powder inhibited progression through S phase in Chinese hamster CHO cells, as measured by flow cytometry (Costa *et al.*, 1982).

Hansen and Stern (1984) reported that nickel powder transformed BHK 21 cells [see General Remarks for concern about this assay]. Proliferation in soft agar was used as the endpoint. At equally toxic doses, they found that nickel powder and crystalline nickel subsulfide had similar transforming activities; the toxicity of 200 μg/ml nickel powder was equal to that of 10 μg/ml nickel subsulfide.

(ii) *Nickel oxides*

Nickel monoxide and nickel trioxide in distilled water gave negative results in the *Bacillus subtilis rec*$^+$*/rec*$^-$ assay for differential toxicity at concentrations ranging from 5 to 50 mM (Kanematsu *et al.*, 1980). [The Working Group noted that since particulate nickel compounds such as these are relatively insoluble and their entry into mammalian cells requires phagocytosis (Costa & Mollenhauer, 1980a,b,c), it is unlikely that they were able to enter the bacteria.]

Chromosomal aberrations were not induced in human peripheral lymphocytes by treatment *in vitro* with nickel monoxide [details not given] (Paton & Allison, 1972).

Nickel monoxide and nickel trioxide transformed Syrian hamster embryo cells at concentrations of 5-20 μg/ml. The activity of the trioxide was about twice that of the monoxide, similar to that of metallic nickel and about 20% that of crystalline nickel sulfide (Costa *et al.*, 1981a,b).

Nickel monoxide that was calcined at a low temperature had greater transforming activity in this system than nickel monoxide calcined at a high temperature at concentrations of 5 and 10 μg/ml and was equivalent to that of crystalline nickel sulfide. The cell-transforming activity of these nickel compounds was reported to correlate well with their ability to induce preneoplastic changes in rats (Sunderman *et al.*, 1987).

Syrian hamster BHK 21 cells were transformed by nickel monoxide and by a nickel oxide catalyst identified as $NiO_{1\cdot4}(3H_2O)$. At equally toxic doses, nickel monoxide had the same transforming activity as did nickel subsulfide. [See General Remarks for concern about this assay.] The nickel oxide catalyst, $NiO_{1\cdot4}$, had similar toxicity and transforming capacity as nickel subsulfide (Hansen & Stern, 1983, 1984).

The ability of 50 μM nickel monoxide to induce anchorage-independent growth in primary human diploid foreskin fibroblasts was similar to that of 10 μM nickel subsulfide or nickel acetate. The absolute numbers of anchorage-independent colonies induced at these doses were 26 with nickel monoxide, 67 with nickel subsulfide, 79 with nickel sulfide (10 μM) and about 42 with nickel acetate, compared with none in cultures of untreated cells. The frequency of anchorage-independent growth induced by nickel monoxide was about three-fold less than with nickel subsulfide, but was equivalent to that obtained with nickel acetate. The tranformed cells had 33- to 429-fold higher plating efficiency in agar than the parental cells; anchorage-independence was stable for eight passages only (Biedermann & Landolph (1987).

Nickel oxide inhibited progression through S phase in Chinese hamster CHO cells, as measured by flow cytometry (Costa *et al.*, 1982).

(iii) *Nickel sulfides (crystalline nickel sulfide, crystalline nickel subsulfide and amorphous nickel sulfide)*

Crystalline nickel sulfide and nickel subsulfide were actively phagocytized by cells at an early stage following their addition to tissue cultures. Phagocytosis was dependent upon the calcium concentration in the medium (Abbracchio *et al.*, 1982a) and particle size (particles >5-6 μm were much less actively taken up and much less toxic than smaller particles) (Costa & Mollenhauer, 1980a,b,c). Particles

are taken up in areas of active cell ruffling, internalized and moved about the cell in a saltatory motion; lysosomes repeatedly interact with the particles, which are contained in the perinuclear region and sometimes inside cytoplasmic vacuoles, where they slowly dissolve, releasing nickel ions (Evans *et al.*, 1982). Interaction between lysosomes and nickel sulfide particles may result in exposure of the particles to the acidic content of the lysosomes, and this interaction may accelerate intracellular dissolution of crystalline nickel sulfide to ionic nickel (Abbracchio *et al.*, 1982a). In contrast, amorphous nickel sulfide and nickel particles were not significantly taken up by cells *in vitro* (Costa *et al.*, 1981a). Crystalline nickel sulfide particles differ from amorphous particles in that they have a negative surface charge, as shown using Z-potential measurements and binding of the particles to filter-paper discs offering different charges (Abbracchio *et al.*, 1982b). Alteration of the positive charge of amorphous nickel sulfide particles by treatment with lithium aluminium hydride results in activation of phagocytosis (Abbracchio *et al.*, 1982b; Costa, 1983).

Crystalline nickel sulfide was actively phagocytized by the protozoan *Paramoecium tetraurelia* and induced lethal genetic damage in parent cells. The activity of nickel subsulfide was more consistent than that of nickel sulfide, but both compounds produced higher mutagenic activities than glass beads, used as a control. The concentrations used ranged from 0.5 to 54 μg/ml; both compounds showed greatest mutagenicity at 0.5 μg/ml, as higher levels were toxic (Smith-Sonneborn *et al.*, 1983).

Crystalline nickel subsulfide at 5, 10 and 50 μg/ml inhibited DNA synthesis in the rat liver epithelial cell line T51B (Swierenga & McLean, 1985). Nickel subsulfide inhibited progression through S phase in Chinese hamster CHO cells, as measured by flow cytometry (Costa *et al.*, 1982).

Crystalline nickel sulfide and nickel subsulfide were active in inducing DNA damage in cultured mammalian cells. Crystalline nickel sulfide induced DNA strand breaks in rat primary hepatocytes (Sina *et al.*, 1983) and, at 1-20 μg/ml, single-strand breaks in tritium-labelled DNA in cultured Chinese hamster ovary cells, as determined using alkaline sucrose gradients (Robison & Costa, 1982). Using the same technique, Robison *et al.* (1982) showed that crystalline nickel subsulfide also induced strand breaks, whereas amorphous nickel sulfide, which is not phagocytized by cells, did not. As observed with alkaline elution analysis, crystalline nickel sulfide induced two major types of lesion — single-strand breaks and DNA protein cross-links (Costa *et al.*, 1982; Patierno & Costa, 1985). Treatment of primary Syrian hamster embryo cells with crystalline nickel subsulfide at 10 μg/ml and Chinese hamster CHO cells with crystalline nickel sulfide at 1-5 μg/ml induced DNA repair, as determined by analysis with caesium chloride gradients. Amorphous nickel sulfide had no effect in either cell type (Robison *et al.*, 1983).

Crystalline nickel subsulfide and amorphous nickel sulfide induced a weak mutation response at the *hprt* (6-thioguanine and 8-azaguanine resistance) locus in Chinese hamster ovary cells (Costa *et al.*, 1980).

Mutation to 8-azaguanine resistance was induced in a cultured rat liver epithelial cell line T51B treated with particulate crystalline nickel subsulfide at concentrations ranging from 5 to 50 μg/ml. At noncytotoxic doses, the mutagenic activity was four-fold above background, and at cytotoxic doses it was 20-fold above background. The mutagenic activity of dissolved products of these particles (at 12.5-20 μg/ml) was about two-fold above background at noncytotoxic doses and 20-fold above background at cytotoxic doses. Neither dissolved nor particulate nickel subsulfide at 2-27 μg/ml induced unscheduled DNA synthesis in rat primary hepatocytes (Swierenga & McLean, 1985). Nickel subsulfide, however, was reported to inhibit unscheduled DNA synthesis induced in primary rat hepatocytes by methyl methane sulfonate [details not given] (Swierenga & McLean, 1985). Concentrations of 0.5-10 μM nickel subsulfide did not induce 8-azaguanine or 6-thioguanine resistance in primary human fibroblasts (Biedermann & Landolph, 1987).

Crystalline nickel sulfide (0.1-0.8 μg/cm^2) was mutagenic in monolayer cultures in Chinese hamster V79 cells in which the endogenous *hprt* gene had been inactivated by a mutation and a single copy of a bacterial *gpt* gene had been inserted (Christie *et al.*, 1990).

The frequency of sister chromatid exchange was increased in cultured human lymphocytes treated with nickel subsulfide at 1-10 μg/ml (Saxholm *et al.*, 1981).

Chromosomal aberrations were induced in cultured mouse mammary carcinoma Fm3A cells following treatment with 4-8$\times 10^{-4}$M crystalline nickel sulfide dissolved in medium and filtered. The early chromosomal aberrations consisted of gaps; following reincubation in control medium after treatment, gaps, breaks, exchanges and other types of aberration were observed (Nishimura & Umeda, 1979; Umeda & Nishimura, 1979). [The Working Group noted that the chemical form of nickel used in this study is not known.]

Treatment of Chinese hamster ovary cells with crystalline nickel sulfide at 5-20 μg/ml for 6-48 h produced a dose- and time-dependent increase in the frequency of chromosomal aberrations, which were selective for heterochromatin and included mostly g ps and breaks, with some exchanges and dicentrics (Sen & Costa, 1985). Crystalli ıe nickel sulfide at 1-10 μg/ml also increased the frequency of sister chromatid e> :hange in a dose-dependent fashion, selectively in heterochromatic regions, in both Chinese hamster ovary cells (Sen & Costa, 1986b) and mouse C3H/10T½ cells (Sen *et al.*, 1987).

A dose-dependent increase in the frequency of morphological transformation was induced in primary Syrian hamster embryo cells by treatment with crystalline nickel subsulfide at 1-5 μg/ml for nine days (DiPaolo & Casto, 1979) and by either crystalline nickel sulfide or nickel subsulfide at 0.1-10 μg/ml for 48 h (Costa *et al.*, 1979; Costa, 1980; Costa & Mollenhauer, 1980a,b,c; Costa *et al.*, 1981a,b, 1982). At the same dose range, amorphous nickel sulfide had no effect. Clones derived from the transformed cells had greater plating efficiency, saturation densities and proliferation rates than normal cells; they also had more inducibility of ornithine decarboxylase, were able to proliferate in soft agar and were tumorigenic in nude mice.

C3H/10T½ cells were transformed at equal frequencies by crystalline nickel subsulfide at concentrations of 0.001, 0.01 and 0.1 μg/ml; at concentrations higher than 1 μg/ml, there was no transformation due to cell lysis or death. Transformed cells also showed long microvilli. They were not characterized for their ability to form tumours in nude mice or for anchorage-independent growth (Saxholm *et al.*, 1981). [The Working Group questioned the induction of transformation by concentrations of crystalline nickel subsulfide as low as 0.001 μg/ml.]

Crystalline nickel subsulfide induced transformed properties in rat liver epithelial T51B cells that were related to cytokeratin lesions. Solutions prepared as leachates of nickel subsulfide (containing about 300 μg/ml Ni) induced large juxtanuclear cytokeratin aggregates within 24 h of exposure, which persisted after removal of the compounds and were passed on to daughter cells. After long-term exposure to 2.5 μg/ml crystalline nickel subsulfide (dissolution products), these lesions were related to concomitant induction of differentiation and transformation markers, loss of density dependence, ability to grow in calcium-deficient medium and increased growth rates. Altered cells formed differentiated benign tumours in nude mice (Swierenga *et al.*, 1989).

Crystalline nickel subsulfide at 5-20 μg/ml induced transformation to anchorage-independence of Syrian hamster BHK 21 cells (Hansen & Stern, 1983). [See General Remarks for concern about this assay.]

Human skin fibroblasts transformed by crystalline nickel subsulfide to anchorage-independent growth had a much higher plating efficiency than normal cells. The phenotype was stable for eight passages (Biedermann & Landolph, 1987).

Crystalline nickel sulfide, but not amorphous nickel sulfide, at doses of 1–20 μg/ml, inhibited the polyriboinosinic-polyribocytidylic acid-stimulated production of α/β interferon in mouse embryo fibroblasts (Sonnenfeld *et al.*, 1983).

Heterochromatic abnormalities were seen in early-passage cultures of cells from crystalline nickel sulfide-induced, mouse rhabdomyosarcomas (Christie *et al.*, 1988).

(iv) *Nickel salts (nickel chloride, nickel sulfate, nickel nitrate and nickel acetate)*

Nickel acetate induced λ prophage in *Escherichia coli* $WP2_s$, with a maximal effect at 0.04 mM (Rossmann *et al.*, 1984). Nickel sulfate at 300 μg/ml did not induce forward mutations in T4 phage (Corbett *et al.*, 1970).

Nickel chloride at 1-10 mM decreased the fidelity of DNA polymerase using a poly (c) template (Sirover & Loeb, 1976, 1977). Nickel acetate inhibited DNA synthesis in mouse mammary carcinoma Fm3A cells (Nishimura & Umeda, 1979).

Nickel chloride at 200-1000 μM induced a genotoxic response in a differential killing assay using *E. coli* WP2 (wild-type) and the repair-deficient derivative WP67 (*uvrA*$^-$, *polA*$^-$) and CM871 (*uvrA*$^-$, *recA*$^-$, *lexA*$^-$) (Tweats *et al.*, 1981). De Flora *et al.* (1984) reported negative results with nickel chloride, nickel nitrate and nickel acetate using the same strains in a liquid micromethod test procedure, with and without an exogenous metabolic system.

Nickel chloride did not induce differential toxicity in *B. subtilis* H17 *rec*$^+$ (*arg*$^-$, *trp*$^-$) or M45 *rec*$^-$ (*arg*$^-$, *trp*$^-$) at 5-500 mM (Nishioka, 1975; Kanematsu *et al.*, 1980). No mutagenicity was induced by nickel chloride at 0.1-100 mM in *S. typhimurium* LT_2 or TA100 (Tso & Fung, 1981), by nickel chloride, nickel acetate or nickel nitrate in *S. typhimurium* TA1535, TA1537, TA1538, TA97, TA98 or TA100 (De Flora *et al.*, 1984) or by nickel chloride or nickel sulfate in *S. typhimurium* TA1535, TA1537, TA1538, TA98 or TA100, when trimethylphosphate was substituted for *ortho*-phosphate to allow nickel to be soluble in the media (Arlauskas *et al.*, 1985). Even when substantial quantities of nickel were demonstrated to enter the bacteria, there was still no mutagenic response in *S. typhimurium* strains TA1535, TA1538, TA1975 or TA1978 (0.5-2 mM) (Biggart & Costa, 1986).

Pikálek and Nečásek (1983), however, demonstrated mutagenic activity of nickel chloride at 0.5-10 μg/ml in homoserine-dependent *Corynebacterium* sp887, utilizing a fluctuation test. Dubins and LaVelle (1986) demonstrated co-mutagenesis of nickel chloride with alkylating agents in *S. typhimurium* strain TA100 and in *E. coli* strains WP2$^+$ and WP2 *uvrA*$^-$; Ogawa *et al.* (1987) demonstrated co-mutagenesis with 9-aminoacridine. Nickel acetate at up to 100 μM was not co-mutagenic with ultraviolet light in *E. coli* WP2 (Rossman & Molina, 1986). Soluble nickel salts have been shown to be negative in host-mediated assays, using *S. typhimurium* G46 in NMRI mice and *Serratia marcescens* A21 in mice, at concentrations of 50 mg/kg (Buselmaier *et al.*, 1972).

Nickel chloride at 3 and 10 mM for 24 h induced gene conversion in *Saccharomyces cerevisiae* D7 (Fukunaga *et al.*, 1982). It also induced petite mutations in 13 *S. cerevisiae* haploid strains (Egilsson *et al.*, 1979).

Negative results were obtained in the *Drosophila melanogaster* somatic eye colour (zeste mutation) test with nickel chloride at 0.21 mM (Rasmuson, 1985) and at 4.2 mM (Vogel, 1976) and with nickel nitrate at 0.14 mM (Rasmuson, 1985).

Nickel sulfate induced sex-linked recessive lethal mutations in *D. melanogaster* at concentrations of 200, 300 and 400 ppm and sex chromosomal loss at the highest concentration tested. The injection volume was not stated, but the LD_{50} was 400 ppm (Rodriguez-Arnaiz & Ramos, 1986). Nickel nitrate at 3.4-6.9 mM did not induce sex-linked recessive lethal mutations in *D. melanogaster* (Rasmuson, 1985).

Nickel chloride increased the frequency of strand breaks in Chinese hamster ovary cells at 1 and 10 μg/ml with 2-h exposure (Robison & Costa, 1982) and at 10-100 μM for 16 and 48 h, with a decrease in the average molecular weight of DNA from 7.2-5.7 $\times$ 10^{-7} Da (Robison *et al.*, 1982). Nickel chloride at 0.5-5 mM induced both single-strand breaks and DNA-protein cross-links in the same cell line. The extent of cross-linking was maximal during the late S phase of the cell cycle when heterochromatic DNA is replicated (Patierno & Costa, 1985; Patierno *et al.*, 1985).

Nickel chloride at 0.05 mM for 30 min did not induce DNA strand breaks in human lymphocytes as evaluated by alkaline unwinding (McLean *et al.*, 1982). [The Working Group noted that the exposure period was very short and the dose very low.] Nickel sulfate at 250 μg/ml did not induce DNA single-strand breaks in human fibroblasts (Ag 1522) (Fornace, 1982).

Nickel chloride at 0.1-1 mM induced DNA repair synthesis in Chinese hamster ovary and primary Syrian hamster embryo cells, which have a very high degree of density inhibition of growth and very little background replication synthesis (Robison *et al.*, 1983, 1984). It inhibited DNA synthesis in primary rat embryo cells at 1.0 μg/ml (Basrur & Gilman, 1967) and in T51B rat liver epithelial cells (Swierenga & McLean, 1985).

Exposure of two human cell lines, HeLa and diploid embryonic fibroblasts, and of Chinese hamster V79 cells and L-A mouse fibroblasts to nickel chloride *in vitro* resulted in a dose-dependent depression of proliferation and mitotic rate. The effects on viability were accompanied by a reduction in DNA, protein and, to a lesser degree, RNA synthesis. Cells in G1 and early S phases were most sensitive (Škreb & Fischer, 1984). Nickel chloride also selectively blocked cell cycle progression in the S phase in Chinese hamster ovary cells (Harnett *et al.*, 1982). Nickel chloride at 40-120 μM for one to several days of exposure prolonged S-phase in Chinese hamster ovary cells (Costa *et al.*, 1982).

Nickel chloride at 0.4 and 0.8 mM for 20 h induced 8-azaguanine-resistant mutations in Chinese hamster V79 cells, although 0.8 mM induced a very weak mutagenic response (Miyaki *et al.*, 1979). Nickel chloride at 0.5-2.0 mM induced a dose-related increase in the frequency of mutation to 6-thioguanine resistance in

Chinese hamster V79 cells. At 2 mM, cell survival was 50% and the mutant fraction was 8.6-fold above background (Hartwig & Beyersmann, 1989). Trifluorothymidine-resistant mutants were induced in L5178Y $tk^{+/-}$ mouse lymphoma cells following exposure to nickel chloride at 0.17-0.71 mM for 3 h; dose-dependent two- to five-fold increases in mutation frequency were seen, survival ranging from 5 to 33.5% (Amacher & Paillet, 1980).

Nickel sulfate at 0.1 mM induced a two-fold increase in the frequency of mutation to 6-thioguanine resistance over the background level in Chinese hamster V79 cells (G12) containing a transfected bacterial *gpt* gene (Christie *et al.*, 1990). No gene mutation to ouabain resistance was seen, however, in primary Syrian hamster embryo cells exposed to 5 μg/ml nickel sulfate (Rivedal & Sanner, 1980).

As assessed in a mutation assay for the synthesis of P-85$^{gag\text{-}mos}$ viral proteins, nickel chloride at concentrations of 20-160 μM induced expression of the v-*mos* gene in MuSVts 110-infected rat kidney cells (6m2 cell line) (Biggart & Murphy, 1988).

Nickel chloride at 0.01-0.05 mM increased the incidence of sister chromatid exchange in Chinese hamster ovary cells (Sen *et al.*, 1987). An increased frequency was also seen with nickel sulfate at 0.1 mM in the P33 $8D_1$ macrophage cell line (Andersen, 1983), at 0.13 mM in Chinese hamster Don cells (Ohno *et al.*, 1982), at 0.004-0.019 mM in Syrian hamster embryo cells (Larramendy *et al.*, 1981), at 0.75 μg/ml (0.003 mM) in Chinese hamster ovary cells (Deng & Ou, 1981) and at 0.01 mM in human lymphocytes (Andersen, 1983). Dose-dependent increases in the frequency of sister chromatid exchange were seen in human peripheral blood lymphocytes with nickel sulfate at 0.01 mM and 0.019 mM (Larramendy *et al.*, 1981), 0.0023-2.33 mM (Wulf, 1980) and 0.95-2.85 μM (Deng & Ou, 1981).

Nickel chloride induced chromosomal aberrations in Fm3A mouse mammary carcinoma cells (Nishimura & Umeda, 1979; Umeda & Nishimura, 1979). It also induced aberrations (primarily gaps, breaks and exchanges) in Chinese hamster ovary cells at 0.001-1 mM, preferentially in heterochromatic regions (Sen & Costa, 1985, 1986b; Sen *et al.*, 1987); and aberrations in Syrian hamster embryo cells at 0.019 mM (Larramendy *et al.*, 1981). Increased frequencies were also reported in Syrian hamster embryo cells (0.019 mM) and human peripheral blood lymphocytes (0.019 mM) exposed to nickel sulfate hexahydrate (Larramendy *et al.*, 1981) and in Fm3A mouse mammary carcinoma cells exposed to nickel acetate at 0.6 mM for 48 h (Umeda & Nishimura, 1979) or at 1 mM for 24 h (Nishimura & Umeda, 1979).

Nickel sulfate at 1.0 mM reduced average chromosomal length in human lymphocytes, indicating its ability to act as a powerful spindle inhibitor at concentrations just below lethal levels (Andersen, 1985).

Nickel sulfate hexahydrate and nickel chloride induced a concentration-dependent increase in morphological transformation of Syrian hamster embryo cells (Pienta *et al.*, 1977; DiPaolo & Casto, 1979 [2.5-10 μg/ml]; Zhang & Barrett, 1988). Nickel sulfate transformed these cells at 5 μg/ml (Rivedal & Sanner, 1980; Rivedal *et al.*, 1980; Rivedal & Sanner, 1981, 1983), and concentrations of 10–40 μg/ml (38-154 μM) nickel sulfate enhanced transformation of normal rat kidney cells infected with Molony murine sarcoma virus (Wilson & Khoobyarian, 1982).

Nickel acetate at 100-400 μg/ml transformed Syrian hamster BHK21 cells (Hansen & Stern, 1983) [See General Remarks for concern about this assay.]

Nickel acetate and nickel sulfate at 10 μM induced transformation to anchorage-dependent growth of primary human foreskin fibroblasts (Biedermann & Landolph, 1987).

Continuous exposure of cultures of normal human bronchial epithelial cells to nickel sulfate at 5-20 μg/ml reduced colony-forming efficiency by 30-80%. After 40 days of incubation, 12 cell lines were derived which exhibited accelerated growth, aberrant squamous differentiation and loss of the requirement for epidermal growth factor for clonal growth. Aneuploidy was induced and marker chromosomes were found. However, none of these transformed cultures was anchorage-independent or produced tumours upon injection into athymic nude mice (Lechner *et al.*, 1984). Human fetal kidney cortex explants were exposed continuously to 5 μg/ml nickel sulfate. After 70-100 days, immortalized cell lines were obtained, with decreased serum dependence, increased plating efficiency, higher saturation density and ability to grow in soft agar. However, they were not tumorigenic (Tveito *et al.*, 1989).

Nickel sulfate disrupted cell-to-cell communication in a dose-related manner in NIH3T3 cells from a base level of 98% at 0.5 mM to 2% at 5mM; cell viability was not affected by these concentrations (Miki *et al.*, 1987). [The Working Group noted that the method for determining cell viability was not described.]

Intraperitoneal injections of nickel sulfate at 15-30% of the LD_{50} to CBA mice *in vivo* suppressed DNA synthesis in hepatic epithelial cells and in the kidney (Amlacher & Rudolph, 1981). Nickel chloride given by intramuscular injection to rats at 20 mg/kg bw Ni inhibited DNA synthesis in the kidney (Hui & Sunderman, 1980).

Polychromatic erythrocytes were not induced in BALB/c mice after an intraperitoneal injection of 25 mg/kg bw nickel chloride or 56 mg/kg bw nickel nitrate (Deknudt & Léonard, 1982).

The frequency of chromosomal aberrations in bone-marrow cells and spermatogonia of male albino rats was not increased following intraperitoneal injections of 3 and 6 mg/kg bw nickel sulfate. Animals were sacrificed seven to 14 days after treatment (Mathur *et al.*, 1978).

Nickel chloride increased the frequency of chromosomal aberrations in bone-marrow cells of Chinese hamsters given intraperitoneal injections of concentrations that were 4-20% of the LD_{50} (Chorvatovičová, 1983) and of Swiss mice given intraperitoneal injections of 6, 12 or 24 mg/kg bw (Mohanty, 1987).

Dominant lethal mutations were not induced in BALB/c mice after an intraperitoneal injection of 12.5-100 mg/kg bw nickel chloride or 28-224 mg/kg bw nickel nitrate (Deknudt & Léonard, 1982).

(v) *Other nickel compounds*

DNA-protein cross-linking in the presence of the nickel[II]- and nickel[III]-tetraglycine complexes and molecular oxygen was observed *in vitro* in calf thymus nucleohistone. The same complexes were also able to cause random polymerization of histones *in vitro* (Kasprzak & Bare, 1989).

Haworth *et al.* (1983) reported no mutation in *S. typhimurium* TA100, TA1535, TA1537 or TA98 following exposure to nickelocene at doses up to 666 μg/plate.

Nickel potassium cyanide at concentrations of 0.2-1.6 mM for 48 h increased the frequency of chromosomal aberrations in Fm3A mouse mammary carcinoma cells (Nishimura & Umeda, 1979; Umeda & Nishimura, 1979).

Crystalline nickel subselenide at 1-5 μg/ml inhibited cell progression through S phase, as seen with flow cytometry (Costa *et al.*, 1982). Concentrations of 5-20 μg/ml crystalline nickel subselenide transformed primary Syrian hamster embryo cells (Costa *et al.*, 1981a,b; Costa & Mallenhauer, 1980c).

Intravenous administration of nickel carbonyl to rats at 20 mg/kg bw Ni inhibited DNA synthesis in liver and kidney (Hui & Sunderman, 1980).

DNA-protein cross-links and single-strand breaks, as detected by alkaline elution, were found in rat kidney nuclei 20 h after intraperitoneal injection of 'nickel carbonate' at 10-40 mg/kg bw (Ciccarelli *et al.*, 1981). After 3 and 20 h, single-strand breaks were detected in lung and kidney nuclei, and both DNA-protein and DNA interstrand cross-links were found in kidney nuclei. No DNA damage was observed in liver or thymus gland nuclei (Ciccarelli & Wetterhahn, 1982). [The Working Group noted that the compound tested was probably basic nickel carbonate.]

3.3 Other relevant data in humans

(*a*) *Absorption, distribution, excretion and metabolism*

Recent reviews include those of Raithel and Schaller (1981), Sunderman *et al.* (1986a), the US Environmental Protection Agency (1986), Grandjean *et al.* (1988), Sunderman (1988) and the World Health Organization (1990).

A positive relation exists between air levels of nickel and serum/plasma concentrations of nickel after occupational exposure to various forms of nickel (see also

Tables 11, 12, 13). A considerable scattering of results was apparent, and the correlation was poor; a better correlation may be achieved in individual studies of well-defined exposure groups (Grandjean *et al.*, 1988). Sparingly soluble compounds may be retained in the lungs for long periods of time. Thus, even three to four years after cessation of exposure, nickel concentrations in plasma and urine were elevated in retired nickel workers exposed to sparingly soluble compounds in the roasting/smelting department of a nickel refinery (Boysen *et al.*, 1984). Respiratory uptake of nickel in welders is described in the monograph on welding.

Provided that pulmonary exposure to nickel can be excluded, the approximate fraction of nickel absorbed by the intestinal tract can be estimated from oral intake and faecal and urinary nickel elimination (Horak & Sunderman, 1973). Cumulative urinary excretion in non-fasting volunteers given a single oral dose of 5.6 mg Ni as nickel sulfate hexahydrate indicated an intestinal absorption of 1-5% (Christensen & Lagesson, 1981; Sunderman, 1988). After ingestion of nickel sulfate during fasting, 4-20% of the dose was excreted in the urine within 24 h (Cronin *et al.*, 1980). Compartmental analysis of nickel levels in serum, urine and faeces in a study of intestinal absorption of nickel sulfate by human volunteers showed that an average of about 27% was absorbed when ingested as an aqueous solution after 12 h of fasting, while 0.7% was absorbed when the nickel was ingested with scrambled eggs (Sunderman *et al.*, 1989b). Ingestion of food items with a high natural nickel content resulted in a urinary excretion corresponding to about 1% of the amount ingested (Nielsen *et al.*, 1987). The bioavailability of nickel can be reduced by various dietary constituents and beverages. Drugs may influence intestinal nickel absorption. Ethylenediaminetetraacetic acid very efficiently prevented intestinal absorption of nickel (Solomons *et al.*, 1982); and, as reported in an abstract, disulfiram increased the intestinal absorption of nickel, probably by forming a lipophilic complex between its metabolite diethyldithiocarbamate and nickel (Hopfer *et al.*, 1984).

After intestinal absorption of nickel ingested as nickel sulfate hexahydrate in lactose by eight volunteers, most of the nickel present in blood was in serum; nickel concentrations in serum and blood showed a very high positive correlation ($r = 0.99$) (Christensen & Lagesson, 1981). In patients with chronic renal failure, a high nickel concentration was found in serum but no significant increase was observed in lymphocytes (Wills *et al.*, 1985). However, in nickel refinery workers, plasma nickel concentrations were lower than those in whole blood, and about 63% appeared to be contained in the buffy coat (Barton *et al.*, 1980).

As reported in an abstract, nickel levels in intercellular fluid were significantly lower in a group of nickel-allergic patients than in controls, possibly due to cell binding or uptake (Bonde *et al.*, 1987). This finding may be related to the observation that incubation with nickel subsulfide *in vitro* caused considerable binding of

nickel to the cell membrane of T-lymphocytes from nickel-sensitized patients but to very few cells from nonsensitized persons (Hildebrand *et al.*, 1987).

The lungs contain the highest concentration of nickel in humans with no known occupational nickel exposure; lower levels occur in the kidneys, liver and other tissues (Sumino *et al.*, 1975; Rezuke *et al.*, 1987). One study documented high levels in the thyroid and adrenals (Rezuke *et al.*, 1987) and another in bone (Sumino *et al.*, 1975). The pulmonary burden of nickel appears to increase with age (Kollmeier *et al.*, 1987), although this correlation was not confirmed in another study (Raithel *et al.*, 1988). The upper areas of the lungs and the right middle lobe contained higher nickel concentrations than the rest of the lung (Raithel *et al.*, 1988), and high concentrations were found in hilar lymph nodes (Rezuke *et al.*, 1987).

Lung tissue from three of four random cases of bronchial carcinoma from an area with particularly high local emissions of chromium and nickel contained increased concentrations of nickel and chromium (Kollmeier *et al.*, 1987), while no such tendency was seen in ten other cases with no known occupational exposure to nickel (Turhan *et al.*, 1985).

High nickel concentrations were found in biopsies of nasal mucosa from both active and retired workers from the Kristiansand, Norway, nickel refinery, particularly in workers from the roasting/smelting department. After retirement, increased nickel levels persisted for at least ten years, with slow release at a half-time of 3.5 years (Torjussen & Andersen, 1979). Biopsies from two nasal carcinomas in nickel refinery workers contained nickel concentrations similar to those seen in biopsies from workers without cancer (Torjussen *et al.*, 1978). Lung tissue obtained at autopsy of workers from the roasting and smelting department of the Norwegian nickel refinery contained higher nickel concentrations (geometric mean, 148 μg/g dry weight; n = 15) than tissue from workers from the electrolysis department (geometric mean, 16 μg/g; n = 24); nickel concentrations in lung tissue were not higher in workers who had died from lung cancer than in workers who had died of other causes (Andersen & Svenes, 1989).

In cases of nickel carbonyl poisoning, the highest nickel concentrations have been recorded in the lungs, with lower levels in kidneys, liver and brain (National Research Council, 1975).

The half-time of nickel in serum was 11 h (one-compartment model during the first 32 h) in eight volunteers after ingestion of 5.6 mg nickel sulfate hexahydrate in lactose; serum nickel concentration and urinary nickel excretion showed a highly positive correlation ($r = 0.98$) (Christensen & Lagesson, 1981). Possibly due to delayed absorption of inhaled nickel, somewhat longer half-times were reported for nickel concentrations in plasma and urine (20-34 h and 17-39 h, respectively) in nickel platers (Tossavainen *et al.*, 1980), glass workers (30-50 h in urine) (Raithel *et*

al., 1982; Sunderman *et al.*, 1986a) and welders (53 h in urine) (Zober *et al.*, 1984). Ten subjects who had accidentally ingested soluble nickel compounds and were treated the following day with intravenous fluids to induce diuresis, showed an average elimination half-time of 27 h, while the half-time was twice as high in untreated subjects with lower serum nickel concentrations (Sunderman *et al.*, 1988b).

Urinary excretion of nickel is frequently used to survey workers exposed to inorganic nickel compounds (Aitio, 1984; Sunderman *et al.*, 1986a; Grandjean *et al.*, 1988). The best indicator of current exposure to soluble nickel compounds is a 24-h urine sample (Sunderman *et al.*, 1986a). In cases of nickel carbonyl intoxication, urinary nickel level is an important diagnostic and therapeutic guide (Sunderman & Sunderman, 1958; Adams, 1980), but its use in biological monitoring of exposure to nickel carbonyl has not been evaluated in detail.

Systemically absorbed nickel may be excreted through sweat (Christensen *et al.*, 1979). Faecal excretion includes non-absorbed nickel and nickel secreted into the gastrointestinal tract (World Health Organization, 1990). Saliva contains nickel concentrations similar to those seen in plasma (Catalanatto & Sunderman, 1977). Secretin-stimulated pancreatic juice was reported to contain an average of 1.09 nmol [64 μg]/ml nickel, corresponding to a total nickel secretion of about 1.64-2.18 μmol [96-128 μg] per day at a pancreatic secretion rate of 1.5-2 l/day (Ishihara *et al.*, 1987). Bile obtained at autopsy contained an average nickel concentration of 2.3 μg/l, suggesting daily biliary excretion of about 2-5 μg (Rezuke *et al.*, 1987). A biliary nickel concentration of 62 μg/g was recorded at autopsy of a small girl who had swallowed about 15 g nickel sulfate crystals (Daldrup *et al.*, 1983); since biliary excretion in this case would correspond to about 0.1% of the dose, it was considered that this route of excretion would be of minimal importance in acute intoxication (Rezuke *et al.*, 1987). Nickel-exposed battery production workers showed high faecal nickel excretion, probably owing to direct oral intake of nickel (e.g., *via* contamination of food from exposed surfaces); faecal nickel content (24 μg/g dry weight) was correlated with the amount present in air (18 μg/m^3) (Hassler *et al.*, 1983).

Nickel was found in cord blood from full-term infants at 3 μg/l (McNeely *et al.*, 1971). Tissue levels at 22-43 weeks of gestation were similar to those seen in adults (Casey & Robinson, 1978).

(*b*) *Toxic effects*

Nickel is an essential nutrient in several species, but no essential biochemical function has been established in humans. Recent reviews of nickel toxicity in humans include those of Raithel and Schaller (1981), the US Environmental Protection Agency (1986), Sunderman (1988) and the World Health Organization (1990).

Acute symptoms reported in 23 patients exposed to severe nickel contamination during haemodialysis included nausea, vomiting, weakness, headache and pal-

pitations; the symptoms disappeared rapidly upon cessation of dialysis (Webster *et al.*, 1980). Twenty workers who accidentally ingested water contaminated with nickel sulfate and chloride hexahydrates at doses estimated at 0.5-2.5 g Ni developed nausea, abdominal pain or discomfort, giddiness, lassitude, headache, diarrhoea, vomiting, coughing and shortness of breath; no related sequela was observed on physical examination, and all individuals were asymptomatic within three days (Sunderman *et al.*, 1988b). In a study of fasting human volunteers, one subject who ingested nickel sulfate (as 50 μg/kg bw Ni) in water developed a transient hemianopsia at the time of peak nickel concentration in serum (Sunderman *et al.*, 1989b). One fatal case of oral intoxication with nickel sulfate has been reported (Daldrup *et al.*, 1983).

Biochemical indications of nephrotoxicity, mainly with tubular dysfunction, have been observed in nickel electrolysis workers (Sunderman & Horak, 1981). Increased haemoglobin and reticulocyte counts were reported in ten subjects three to eight days after they had accidentally ingested 0.5-2.5 g Ni as nickel sulfate and chloride hexahydrates in contaminated drinking-water (Sunderman *et al.*, 1988b).

Nickel is a common skin allergen—in recent studies, the most frequent cause of allergic contact dermatitis in women and one of the most common causes in men; about 10-15% of the female population and 1-2% of males show allergic responses to nickel challenge (Peltonen, 1979; Menné *et al.*, 1982). Nickel ions are considered to be exclusively responsible for the immunological effects of nickel (Wahlberg, 1976). Sensitization appears to occur mainly in young persons, usually due to non-occupational skin exposures to nickel alloys (Menné *et al.*, 1982). Subsequent provocation of hand eczema may be caused by occupational exposures, especially to nickel-containing fluids and solutions (Rystedt & Fischer, 1983). Oral intake of low doses of nickel may provoke contact dermatitis in sensitized individuals (Veien *et al.*, 1985). Inflammatory reactions to nickel-containing prostheses and implants may occur in nickel-sensitive individuals (Lyell *et al.*, 1978).

Several cases of nickel-associated asthma have been described (Cirla *et al.*, 1985). Case reports suggest that inhalation of nickel dusts may result in chronic respiratory diseases (asthma, bronchitis and pneumoconiosis) (Sunderman, 1988). [The Working Group was unable to determine the causal significance of nickel in this regard.]

Nickel carbonyl is the most acutely toxic nickel compound. Symptoms following nickel carbonyl intoxication occur in two stages, separated by an almost symptom-free interval which usually lasts for several hours. Initially, the major symptoms are nausea, headache, vertigo, upper airway irritation and substernal pain, followed by interstitial pneumonitis with dyspnoea and cyanosis. Prostration, pulmonary oedema, kidney toxicity, adrenal insufficiency and death may occur in severe cases (Sunderman & Kincaid, 1954; Vuopala *et al.*, 1970; Sunderman, 1977).

Frequent clinical findings included fever with leukocytosis, electrocardiographic abnormalities suggestive of myocarditis and chest X-ray changes (Zhicheng, 1986). Hyperglycaemia has also been reported (Sunderman, 1977). Neurasthenic signs and weakness may persist in survivors for up to six months (Zhicheng, 1986).

(*c*) *Effects on reproduction and prenatal toxicity*

No data were available to the Working Group.

(*d*) *Genetic and related effects*

Cytogenetic studies have been performed using peripheral blood lymphocytes from electroplating and nickel refining plant workers; they are summarized in Appendix 1 to this volume.

Waksvik and Boysen (1982) found elevated levels of chromosomal aberrations (mainly gaps; $p < 0.003$), but not of sister chromatid exchanges, in two groups of nickel refinery workers. One group of nine workers engaged in crushing/roasting/smelting processes and exposed mainly to nickel monoxide and nickel subsulfide for an average of 21.2 years (range, 3-33 years) at an air nickel content of 0.5 mg/m^3 (range, 0.1-1.0 mg/m^3) and with a mean plasma nickel level of 4.2 µg/l had 11.9% of metaphases with gaps. Another group of workers, engaged in electrolysis, who were exposed mainly to nickel chloride and nickel sulfate for an average of 25.5 years (range, 8-31 years) at an air nickel content of 0.2 mg/m^3 (range, 0.1-0.5 mg/m^3) and with a mean plasma level of 5.2 µg/l, had 18.3% of metaphases with gaps[1]. Mean control values of 3.7% of metaphases with gaps were seen in seven office workers in the same plant with plasma nickel levels of 1 µg/l, who were matched for age and sex. All subjects were nonsmokers and nonalcohol consumers, were free from overt viral disease, were not known to have cancer and had not received therapeutic radiation; none was a regular drug user and the groups were uniform as to previous exposure to diagnostic X-rays.

Waksvik *et al.* (1984) investigated nine ex-workers from the same plant who had been retired for an average of eight years who had had similar types of exposure to more than 1 mg/m^3 atmospheric nickel for 25 years or more; they were selected from among a group of workers known to have nasal dysplasia and who still had plasma nickel levels of 2 µg/l plasma. These retired workers showed some retention of gaps ($p < 0.05$) and an increased frequency of chromatid breaks to 4.1% of metaphases *versus* 0.5% ($p < 0.001$) in 11 unexposed retired workers controlled for age, life style and medication status. All subjects were of similar socioeconomic status and had

[1]The exposures of these workers were clarified in an erratum to the original article, published subsequently (*Mutat. Res.*, *104*, 395 (1982)).

not had X-rays or overt viral disease recently; none smoked or drank alcohol. Four exposed and nine unexposed subjects were on medication but not with drugs known to influence chromosomal parameters.

Deng *et al.* (1983, 1988) studied the frequencies of sister chromatid exchange and chromosomal aberrations in lymphocytes from seven electroplating workers exposed to nickel. Air nickel concentrations were 0.0053-0.094 mg/m^3 (mean, 0.024 mg/m^3). Control subjects were ten administrative workers from the same plant matched for age and sex; the groups were uniform as to socioeconomic status, and none of the subjects smoked or used alcohol, had overt viral disease, had recently been exposed to X-rays or was taking medication known to have chromosomal effects. The exposed workers had an increased frequency of sister chromatid exchange (7.50 $\pm$ 2.19 (SEM) *versus* 6.06 $\pm$ 2.30 (SEM); $p < 0.05$). [The Working Group noted that this is a small difference between groups.] The frequency of chromosomal aberrations (gaps, breaks and fragments) was increased from 0.8% of metaphases in controls to 4.3% in nickel platers.

The frequencies of sister chromatid exchange and chromosomal aberrations were studied in workers in a nickel carbonyl production plant. The subjects were divided into four groups: exposed, exposed smokers, controls and control smokers. Controls were ex-employees. None of the subjects had a history of serious illness; none was receiving irradiation or was infected by viruses at the time of blood sampling. No significant difference in the frequency of chromosomal breaks or gaps was observed between the different groups, and there was no statistically significant difference in the frequency of sister chromatid exchange between unexposed and nickel-exposed workers (Decheng *et al.*, 1987). [The Working Group noted that several discrepancies in the description of this study make it difficult to evaluate.]

Studies of mutagenicity and chromosomal effects in humans are summarized in Table 25.

3.4 Epidemiological studies of carcinogenicity to humans

(*a*) *Introduction*

The report of the International Committee on Nickel Carcinogenesis in Man (ICNCM) (1990) presents updated results on nine cohort studies and one case-control study of nickel workers, one of which was previously unpublished. The industries include mining, smelting, refining and high-nickel alloy manufacture and one industry in which pure nickel powder was used. The report adds to or supersedes previous publications on most of these cohorts, as various new analyses are included, some cohorts have been enlarged, and follow-up has been extended. Nickel species were divided into four categories: metallic nickel, oxidic nickel, soluble nickel and sulfidic nickel (including nickel subsulfide). Soluble nickel was defined as

Table 25. Cytogenetic studies of people exposed occupationally to nickel and nickel compounds

Occupational exposure	Reported principal components	Mean reported dose (range)	Sister chromatid exchange	Chromosomal aberrations	Reference
Crushing, roasting, smelting	Nickel monoxide, nickel subsulfide	Air: 0.5 (0.1–1.0) mg/m³ Exposure: 21.2 (3–33) years	None	Only gaps	Waksvik & Boysen (1982)
Electrolysis	Nickel chloride, nickel sulfate	Air: 0.2 (0.1–0.5) mg/m³ Exposure: 25.2 (8–31) years	None	Mainly gaps	Waksvik & Boysen (1982)
Crushing, roasting, smelting and/or electrolysis	Nickel monoxide, nickel subsulfide, nickel chloride, nickel sulfate	Air: 1 mg/m³ Exposure: > 25 years	None	Gaps and breaks in retired workers	Waksvik *et al.* (1984)
Nickel carbonyl production	Nickel carbonyl	Exposure: 7971 h	None	None	Decheng *et al.* (1987)
Electroplating	Nickel and chromium compounds	Air: 0.0053–0.094 mg/m³ Exposure: 2–27 years	Small increase	Mainly gaps, but also breaks and fragments	Deng *et al.* (1983, 1988)

consisting 'primarily of nickel sulfate and nickel chloride but may in some estimates include the less soluble nickel carbonate and nickel hydroxide'.

The historical estimates of exposure cited in the reviews of the following studies were not based on contemporary measurements. Furthermore, total airborne nickel was estimated first, and this estimate was then divided into estimates for four nickel species (metallic, oxidic, sulfidic and soluble), as defined in the report of the committee (ICNCM, 1990). The procedures for dividing the exposure estimates are described in section 2 of this monograph (pp. 297-298). Because of the inherent error and uncertainties in the procedures for estimating exposures, the estimated concentrations of nickel species in workplaces in the ICNCM analysis must be interpreted as broad ranges indicating only estimates of the order of magnitude of the actual exposures.

In order to facilitate the interpretation of the epidemiological findings on mortality from lung cancer and nasal cancer, selected estimates of exposure are presented in Tables 26, 27 and 28 (pp. 402-404) for some of the plants and subcohorts. The exposure estimates presented in the tables should be used only to make qualitative comparisons of exposure among departments within a plant and should not be used to make comparisons of exposure estimates among plants, for the reasons given above.

(*b*) *Nickel mining, smelting and refining*

(i) *INCO Ontario, Canada (mining, smelting and refining)*[1]

Follow-up of all sinter plant workers and of all men employed at the Ontario division of INCO for at least six months and who had worked (or been a pensioner) between 1 January 1950 and 31 December 1976 (total number of men, 54 509) was extended to the end of 1984 by record linkage to the Canadian Mortality Data Base (ICNCM, 1990). Sinter plant workers included men who had worked in two different sinter plants in the Sudbury area (the Coniston and Copper Cliff sinter plants) and in the leaching, calcining and sintering department at the Port Colborne nickel refinery. In the Coniston sinter plant, sulfidic nickel ore concentrates were partially oxidized at 600°C (Roberts *et al.*, 1984) on sinter machines to remove about one-third of the sulfur and to agglomerate the fine material for smelting in a blast furnace. In the Copper Cliff sinter plant, nickel subsulfide was oxidized to nickel oxide at very high temperatures (1650°C). The leaching, calcining and sintering

[1]There are some discrepancies between the figures cited here and those reported by Roberts *et al.* (1990a,b), but the differences are not substantial.

department produced black and green nickel oxides from nickel subsulfide by a series of leaching and calcining operations. The department also included a sinter plant like that at Copper Cliff. Employment records for men employed in the department did not allow them to be assigned to individual leaching, calcining or sintering operations. Mortality up to the end of 1976 in this cohort of about 55 000 men was described by Roberts *et al.* (1984); an earlier study of 495 men employed at the Copper Cliff sinter plant was reported by Chovil *et al.* (1981). The nickel species to which men were exposed in dusty sintering operations were primarily oxidic and sulfidic nickel, and possibly soluble nickel at lower levels (see Table 26). High concentrations of nickel compounds were estimated in the Copper Cliff sinter plant, which ranged from 25-60 mg/m^3 Ni as nickel oxide and 15-35 mg/m^3 Ni as nickel subsulfide, with up to 4 mg/m^3 Ni soluble nickel as anhydrous nickel sulfate between 1948 and 1954. Among the 3769 sinter plant workers, there were 148 lung cancer deaths (standardized mortality ratio (SMR), 261; 95% confidence interval (CI), 220-306) and 25 nasal cancer deaths (SMR, 5073; 95% CI, 3282-7489). Among the 50 977 nonsinter workers in the cohort, there were 547 lung cancer deaths (SMR, 110; 95% CI, 101-120) and six nasal cancer deaths (SMR, 142; 95% CI, 52-309). The only other site for which cancer mortality was significantly elevated was the buccal cavity and pharynx (12 deaths in sinter plant workers: SMR, 211; 95% CI, 109-369; 35 deaths in other workers: SMR, 71; 95% CI, 49-99). The sinter plant workers had little or no excess risk during the first 15 years after starting work (no nasal cancer death; five lung cancer deaths; SMR, 158 [95% CI, 51-370]), and their subsequent relative risk increased with increasing duration of employment. There were also statistically significant excesses of mortality from lung cancer in men employed for 25 or more years in the Sudbury area, both in mining (129 deaths; SMR, 134 [95% CI, 112-159]) and in copper refining (24 deaths; SMR, 207 [95% CI, 133-308]). In the electrolysis department of the Port Colborne plant, workers were estimated to be exposed to low concentrations of metallic, oxidic, sulfidic and soluble nickel. Seven nasal cancer deaths occurred (SMR, 5385; 95% CI, 2165-11 094) in men who had spent over 15 years in the electrolysis department at Port Colborne; all seven had spent some time in the leaching, sintering and calcining area at the Sudbury site, although two had spent only three and seven months, respectively. Lung cancer mortality among workers in the electrolysis department with no exposure in leaching, calcining and sintering, but with 15 or more years since first exposure, gave an SMR of 88 (19 deaths; 95% CI, 53-137). There was a marked difference in the ratio of lung to nasal cancer excess between the Copper Cliff sinter plant and the Port Colborne leaching, calcining and sintering plant: 7:1 at Copper Cliff (63 observed lung cancers, minus 20.5 expected, *versus* six nasal cancers) and only about 2:1 at Port Colborne (72 observed lung cancers, minus 30.0 expected, *versus* 19 nasal cancers).

(ii) *Falconbridge, Ontario, Canada (mining and smelting)*

A cohort of 11 594 men employed at Falconbridge, Ontario, between 1950 and 1976, with at least six months' service, was previously followed up to the end of 1976 (Shannon *et al.*, 1984a,b). Follow-up has now been extended to the end of 1985 by record linkage to the Canadian Mortality Data Base (ICNCM, 1990). Expected numbers were calculated from Ontario provincial death rates. One death was due to nasal cancer, compared with 0.77 expected. The only cause of death showing a statistically significant excess in the overall analysis was lung cancer (114 deaths; SMR, 135; 95% CI, 111-162). Subdivision of the total cohort by duration of exposure in different areas and latency revealed no SMR for lung cancer that differed significantly from this moderate overall excess, but the highest SMRs occurred in men who had spent more than five years in the mines (46 deaths; SMR, 158; 95% CI, 116-211) or in the smelter (15 deaths; SMR, 163; 95% CI, 91-269). Men who had worked in the smelter are reported to have had low levels of exposure to pentlandite and pyrrhotite, sulfidic nickel, oxidic nickel and some exposure to nickel sulfate. Estimated total exposures to nickel in all areas of the facility were below 1 mg/m^3 Ni (ICNCM, 1990).

(iii) *INCO, Clydach, South Wales, UK (refining)*

The excess of lung and nasal sinus cancer among workers in the INCO refinery in Clydach, South Wales, which opened in 1902, was recognized over 50 years ago (Bridge, 1933). The first formal analyses of cancer mortality were carried out by Hill in 1939 and published by Morgan (1958), who identified calcining, furnaces and copper sulfate extraction as the most hazardous processes. Subsequent reports indicated that the risk had been greatly reduced by 1925 or 1930 (Doll, 1958; Doll *et al.*, 1970, 1977; Cuckle *et al.*, 1980); trends in risk with age at first exposure, period of first exposure and latency were analysed (Doll *et al.*, 1970; Peto *et al.*, 1984; Kaldor *et al.*, 1986). The cohort of 845 men employed prior to 1945 studied by Doll *et al.* (1970) has now been extended to include 2521 men employed for at least five years between 1902 and 1969, and followed up to the end of 1984 (ICNCM, 1990). Among 1348 men first employed before 1930 there were 172 lung cancer deaths (SMR, 393; 95% CI, 336-456) and 74 nasal cancer deaths (SMR, 21 120; 95% CI, 16 584-26 514); the highest risks were associated with calcining, furnaces and copper sulfate production. The calcining and furnace areas had high estimated levels of oxidic, sulfidic and metallic nickel (see Table 27). Until the late 1930s, the oxidic nickel consisted of nickel-copper oxide. Men in the copper plant were exposed to very high concentrations of nickel-copper oxide; they were also exposed to soluble nickel: the extraction of copper from the calcine involved the handling of large volumes of solutions containing 60 g/l nickel as nickel sulfate. Until 1923, arsenic present in sulfuric acid is believed to have accumulated at significant levels in several process departments,

mainly as nickel arsenides. The only other significantly elevated risks were an excess of five lung cancer deaths (SMR, 333; 95% CI, 108-776) and four nasal cancer deaths (SMR, 36 363; 95% CI, 9891-93 089) in men employed before 1930 with less than one year in calcining, furnace or copper sulfate but over five years in hydrometallurgy, an area in which exposure to soluble nickel was similar to that in other high-risk areas and exposures to oxidic nickel were an order of magnitude lower than in other high-risk areas, with negligible exposure to sulfidic nickel (see Table 27); and in the small subgroup of nickel plant cleaners (12 lung cancer deaths; SMR, 784 [95% CI, 402-1361]), who were highly exposed to metallic nickel (5 mg/m^3 Ni), oxidic nickel (6 mg /m^3 Ni) and sulfidic nickel (> 10 mg/m^3 Ni), with negligible exposure to soluble nickel (ICNCM, 1990). A notable anomaly in the data for the whole refinery was the marked reduction in nasal cancer but not lung cancer mortality, when comparing men first exposed before 1920 and those first exposed between 1920 and 1925 (Peto *et al.*, 1984). The risk, although greatly reduced, may not have been entirely eliminated by 1930, as there were 44 lung cancers (SMR, 125 [95% CI, 91-168]) and one nasal cancer (SMR, 526 [95% CI, 13-3028]) among the 1173 later employees.

(iv) *Falconbridge, Kristiansand, Norway (refining)*

The cohort of 3250 men reported by ICNCM (1990) is restricted to men first employed in 1946-69 with at least one year's service and followed until the end of 1984. For each work area, average concentrations for the four categories of nickel (sulfidic nickel, metallic nickel, oxidic nickel and soluble nickel) were estimated as four ranges for three periods (1946-67, 1968-77 and 1978-84). The four ranges and the arithmetic average computed for each range were: low (0.3 mg/m^3), medium (1.3 mg/m^3), high (5 mg/m^3) and very high (10 mg/m^3). There were 77 lung cancer deaths (SMR, 262; 95% CI, 207-327), three nasal cancer deaths (SMR, 453; 95% CI, 93-1324) and a further four incident cases of nasal cancer. Five of the nasal cancer cases had spent their entire employment in the roasting, smelting and calcining department, where oxidic nickel was estimated to have been the predominant exposure, with lesser amounts of sulfidic and metallic nickel. Before 1953, arsenic was present in the feed materials, and significant contamination with nickel arsenides is believed to have occurred at various steps of the process. The remaining two cases were in electrolysis workers who were exposed mainly to soluble nickel (nickel sulfate until 1953 and nickel sulfate and nickel chloride solutions thereafter) and nickel-copper oxides. No other type of cancer occurred significantly in excess. Among men first employed after 1955, there have been 13 lung cancer deaths (SMR, 173 [95% CI, 92-296]) and no nasal cancer (0.2 expected). Several comparisons were made assuming 15 years' latency. The highest risk for lung cancer was seen among a group of workers who had worked in the electrolysis deparment but never in roast-

ing and smelting (30 deaths; SMR, 385; 95% CI, 259-549). In the group of workers who had worked in roasting and smelting but never in the electrolysis department, 14 lung cancer deaths were seen (SMR, 225; 95% CI, 122-377) (see also Table 28). In those who had spent no time in either of these departments, the SMR was 187 (six cases [95% CI, 68-406]). Although exposure to soluble nickel in the roasting, calcining and smelting department was initially estimated to be negligible, it was noted that soluble nickel was certainly present in the Kristiansand roasting department in larger amounts than had been allowed for, and to some extent in all smelter and calcining plants (ICNCM, 1990).

The overlapping cohort reported by Pedersen *et al.* (1973) and Magnus *et al.* (1982) included 2247 men employed for at least three years from when the plant began operation in 1910. Results for cancers diagnosed up to 1979 were presented by Magnus *et al.* (1982). There were 82 lung cancers [standardized incidence ratio (SIR), 373; 95% CI, 296-463] and 21 nasal cancers (SIR, 2630 [95% CI, 1625-4013]). Of the nasal cancers, eight occurred in men involved in roasting-smelting, eight in electrolysis workers, two in workers in other specified processes and three in administration, service and unspecified workers. The incidence of no other type of cancer was significantly elevated overall, although there were four laryngeal cancers (SIR, 670) among roasting and smelting workers. An analysis of lung cancer incidence in relation to smoking suggested an additive rather than a synergistic effect. Adjustment for national trends in lung cancer rates, assuming an additive effect of nickel exposure, suggested little or no reduction in lung cancer risk between men first employed in 1930-39 and those first employed in 1950-59. This contrasts with the marked reduction in nasal cancer risk.

(v) *Hanna Mining and Nickel Smelting, Oregon, USA*

A total of 1510 men who had worked for at least six months between 1953, when the plant opened, and 1977 were followed up to the end of 1983 (ICNCM, 1990). Expected numbers of deaths were those for the state of Oregon. A statistically significant excess of lung cancer was observed among men with less than one year of exposure (seven deaths; SMR, 265 [95% CI, 107-546]) but not in men with longer exposure (20 deaths; SMR, 127 [95% CI, 77-196]) or in the subgroup who had worked in areas with potentially high exposures (smelting, 'skull plant', refining and ferrosilicon plant; seven deaths; SMR, 113; 95% CI, 45-233). There was no nasal cancer, and no excess of other cancers (21 deaths; SMR, 65 [95% CI, 41-100]). Average airborne concentrations were estimated to have been 1 mg/m^3 Ni or less, even in areas with potentially high exposure, and in most areas were below 0.1 mg/m^3 Ni. The principal nickel compounds to which workers were exposed were nickel-containing silicate ore and iron-nickel oxide, with very little soluble nickel and no sulfidic nickel.

(vi) *Societé Le Nickel, New Caledonia (mining and smelting)*

Approximately 25% of the adult male population of New Caledonia has worked in nickel mines (silicate-oxide nickel ores) or smelters. Since the local rates for cancer of the lung and upper respiratory tract are higher than those in neighbouring islands, a small hospital-based case-control study was conducted (Lessard *et al.*, 1978). Of the 68 cases identified in 1970-74, 29 cases and 22/109 controls had been exposed to nickel, giving an age- and smoking-adjusted relative risk (RR) of 3.0. [The Working Group noted that control subjects were selected from among patients seen in the laboratory of one hospital, while cases were identified through a variety of sources. Selection bias could have contributed to the apparent excess risk.]

Another study showed no difference in the incidence of lung cancer (RR, 0.9, not significant) or of upper respiratory tract cancer (RR, 1.4; not significant) between nickel workers and the general population. In a case-control study conducted among the nickel workers, no association was found between cancers at these sites and exposure to total dust, nickeliferous dust, raw ore or calcined ore (Goldberg *et al.*, 1987). Subsequent analyses (Goldberg *et al.*, 1990) provided little evidence that people with lung and upper respiratory tract cancer had had greater exposure to nickel than controls. Exposure was principally to silicate oxides, complex oxides, sulfides, metallic iron-nickel alloy and soluble nickel. The estimated total airborne nickel concentration in the facility was estimated to be low (< 2 mg/m^3 Ni) (ICNCM, 1990).

(vii) *Other studies of mining, smelting and refining*

Several studies have been published in which the results were not described in sufficient detail for evaluation. Saknyn and Shabynina (1970, 1973) reported elevated lung cancer mortality among process workers in four nickel smelters in the USSR (SMRs, 200, 280, 380, 400 [no observed numbers given]). Electrolysis workers, exposed mainly to nickel sulfate and nickel chloride, were reported to be at particularly high risk for lung cancer (SMR, 820); excesses of stomach cancer and soft-tissue sarcoma were also observed. Tatarskaya (1965, 1967) reported an excess of nasal cancer among electrolysis workers in the USSR.

Olejár *et al.* (1982) reported a marginal excess of lung cancer (based on eight cases) among workers in a Czechoslovak refinery.

One nasal sinus cancer and one lung cancer occurred among 129 men at the Outokumpu Oy refinery in Finland, but expected numbers were not calculated. Workers were exposed primarily to soluble nickel; the highest measurement recorded was 1.1 mg/m^3 Ni (ICNCM, 1990).

Egedahl and Rice (1984) found no excess risk among workers in a refinery in Alberta, Canada, but there were only two cases of lung cancer in the cohort (SIR, 83 [95% CI, 10-301]).

(c) *Nickel alloy and stainless-steel production*

(i) *Huntington Alloys (INCO), W. Virginia (refining and manufacture of high-nickel alloys)*

A cohort of 3208 men with at least one year's service before 1947 was followed up to the end of 1977 (Enterline & Marsh, 1982) and then to the end of 1984 (ICNCM, 1990). Workers were exposed to metallic, oxidic, sulfidic and soluble nickel at low levels, except in the calcining department where high levels of sulfidic nickel (4000 mg/m^3 Ni) were present. Average airborne exposures were estimated to have been below 1 mg/m^3 Ni in all areas except calcining. On the basis of the ICNCM report (1990), there was no significant overall excess of lung cancer (91 deaths; SMR, 97 [95% CI, 80-121]). There was a nonsignificant excess among men first employed before 1947 (when calcining ceased) with 30 or more years' service (40 deaths; SMR, 124; 95% CI, 88-169). The group who had worked in calcining for five or more years was too small for useful analysis (two lung cancers; SMR, 100; 95% CI, 12-361). Four deaths from nasal cancer occurred in the whole cohort, all in persons employed before 1948; two were coded on death certificates as nasal cancer (expected, 0.9) and two were classified on the death certificates as bone cancer. Two had not worked in calcining and three had never been exposed to nickel sulfides; one had also worked as a heel finisher in a shoe factory. There was no excess mortality from nonrespiratory cancers.

(ii) *Henry Wiggin, UK (high-nickel alloy plant)*

Mortality up to 1978 in a cohort of 1925 men employed for at least five years in a plant that opened in 1953 was reported by Cox *et al.* (1981). Follow-up has now been extended to April 1985 for 1907 men (ICNCM, 1990). Average exposures from 1975 on rarely exceeded 1 mg/m^3 Ni in any area, with an overall average of the order of 0.5 mg/m^3 Ni. Measurements taken since 1975 were stated probably to be underestimates of the level of exposure to oxidic and metallic nickel of workers in earlier periods. Soluble nickel was reported to constitute 14-49% of total nickel in various departments (Cox *et al.*, 1981). Thirty deaths were due to lung cancer (SMR, 98; 95% CI, 57-121), including 13 deaths among men employed for ten years or more in areas where they were exposed to nickel (SMR, 91; 95% CI, 57-149). Subdivision by duration of exposure or latency produced no evidence of increased lung cancer risk, and there was no nasal cancer. An excess of soft-tissue sarcoma was found, based on two cases (SMR, 769; 95% CI, 92-2769) (ICNCM, 1990).

(iii) *Twelve high-nickel alloy plants in the USA*

Mortality up to the end of 1977 among 28 261 workers (90% male) employed for at least one year in 12 high-nickel alloy plants in the USA, and still working at some time between 1956 and 1960, was reported by Redmond (1984). There were 332 lung cancer deaths (SMR, 109 [95% CI, 98-122]) and two nasal sinus cancer deaths (SMR, 93 [95% CI, 12-358]). The excess of lung cancer was confined to men employed for five or more years in 'allocated services', most of whom were maintenance workers (197 deaths; SMR, 127 [95% CI, 110-146]). Excess mortality was observed from liver cancer (31 deaths; SMR, 182 [95% CI, 124-259]) in all men, and from cancer of the large intestine (SMR, 223 [95% CI, 122-375]) among non-white men. No data on exposure were available, but the authors noted that there may have been exposure to asbestos in these plants.

(iv) *Twenty-six nickel-chromium alloy foundries in the USA*

A proportionate mortality analysis of 851 deaths among men ever employed in 26 nickel-chromium alloy foundries in the USA in 1968-79 (Cornell & Landis, 1984) showed no statistically significant excess of lung cancer (60 deaths; proportionate mortality ratio (PMR, 105 [95% CI, 80-135]) or other cancers (103 deaths; PMR, 87 [95% CI, 71-106]) in comparison with US males. No death was due to nasal cancer.

Lung cancer mortality in a cohort of foundry workers was investigated by Fletcher and Ades (1984). The cohort consisted of men hired between 1946 and 1965 in nine steel foundries in the UK and employed for at least one year. The 10 250 members of the cohort were followed up until the end of 1978 and assigned to 25 occupational categories according to information from personnel officers. Lung cancer mortality for the subcohort of fettlers and grinders in the fettling shop was higher than expected on the basis of mortality rates for England and Wales (32 cases; SMR, 195; 95% CI, 134-276). [The Working Group noted that these workers may have been exposed to chromium- and nickel-containing dusts.]

(v) *Seven stainless-steel and low-nickel alloy production plants in the USA*

A proportionate mortality analysis of 3323 deaths among white males ever employed in areas with potential exposure to nickel in seven stainless-steel and low-nickel alloy production plants (Cornell, 1984) showed no excess of lung cancer (218 deaths; PMR, 97 [95% CI, 85-111]) or of other cancers (419 deaths; PMR 91 [95% CI, 83-100]). There was no death from nasal cancer.

(*d*) *Other industrial exposures to nickel*

(i) *Two nickel-cadmium battery factories in the UK*

Kipling and Waterhouse (1967) reported an excess of prostatic cancer based on four cases among 248 men exposed for one year or longer in a nickel-cadmium bat-

tery factory. The cohort was enlarged to include 3025 workers (85% men) employed for at least one month (Sorahan & Waterhouse, 1983, 1985), and the most recent report included deaths up to the end of 1984 (Sorahan, 1987). Exposure categories were defined on the basis of exposure to cadmium. The authors commented that almost all jobs with high exposure to cadmium also entailed high exposure to nickel hydroxide, and there was also possible exposure to welding fumes (Sorahan & Waterhouse, 1983). The excess of prostatic cancer cases was confined to highly exposed workers, among whom there were eight cases (SIR, 402 [95% CI, 174-792]); in the remainder of the cohort there were seven (SIR, 78 [95% CI, 31-160]) (Sorahan & Waterhouse, 1985). An excess of cancer of the lung was seen (110 deaths; SMR, 130 [95% CI, 107-157]), and this showed a significant association with duration in 'high exposure' jobs, particularly among men first employed before 1947 (Sorahan, 1987).

(ii) *A nickel-cadmium battery factory in Sweden*

A total of 525 male workers in a Swedish nickel-cadmium battery factory employed for at least one year were followed up to 1980 (Andersson *et al.*, 1984). Six deaths were due to lung cancer (SMR, 120 [95% CI, 44-261]), four to prostatic cancer (SMR, 129 [95% CI, 35-330]) and one to nasopharyngeal cancer (SMR, > 1000). Cadmium levels prior to 1950 were said to have been about 1 mg/m^3 in some areas; nickel levels were reported as 'about five times higher', although no actual measurement was reported.

(iii) *A nickel and chromium plating factory in the UK*

A total of 2689 workers (48% male) employed in a nickel-chromium plating factory in the UK were followed to the end of 1983 by Sorahan *et al.* (1987). There was excess mortality from lung cancer (72 deaths; SMR, 150 [95% CI, 117-189]) and nasal cancer (three deaths; SMR, 1000 [95% CI, 206-2922]), but this was confined to workers whose initial employment had been as chrome bath platers, and the lung cancer excess was significantly related to duration of chrome bath work. An earlier study of 508 men employed only as nickel platers in the factory (Burges, 1980) showed no excess for any cancer except that of the stomach (eight deaths; SMR, 267); among men with more than one year's employment, the SMR for stomach cancer was 476 (adjusted for social class and region; four deaths [95% CI, 130-1219]). The SMR for lung cancer was 122 [95% CI, 59-224].

(iv) *A die-casting and electroplating plant in the USA*

A proportionate mortality analysis of 238 deaths (79% male) in workers employed for at least ten years in a die-casting and electroplating plant in the USA was reported by Silverstein *et al.* (1981). There was excess mortality from lung cancer (28 deaths; PMR 191 [95% CI, 127-276]) among white men, but not for cancer at any other site. The PMRs for lung cancer by duration of employment were 165 (< 15

years) and 209 (≥15 years), and those by latency were 178 (<22.5 years) and 211 (≥ 22.5 years). The authors noted that the workers had been exposed to chromium[VI], polycyclic aromatic hydrocarbons and various compounds of nickel.

(v) *Oak Ridge gaseous diffusion plant, Tennessee, USA*

Fine pure nickel powder is used as barrier material in uranium enrichment by gaseous diffusion. A cohort of 814 white men employed at any time before 1954 in the production of this material was followed up from 1948 to 1972 by Godbold and Tompkins (1979). Exposure was thus entirely to metallic nickel. Follow-up was extended to the end of 1977 by Cragle *et al.* (1984), and mortality up to the end of 1982 was reported by ICNCM (1990). The median concentration of nickel was about 0.13 mg/m^3, but high concentrations occurred in some areas. About 300 of the 814 men had been employed for a total of less than two years. There was no excess of lung cancer, either overall (nine deaths; SMR, 54; 95% CI, 25-103) or among men employed for 15 years or longer (five deaths; SMR, 109 [95% CI, 35-254]), and mortality from other cancers was close to that expected (29 deaths; SMR, 96 [95% CI, 64-137]) for the whole cohort. No death from nasal cancer occurred, but only 0.22 were expected. [The Working Group noted that measurements made in 1948-63 (Godbold & Tompkins, 1979) suggest that the average exposure may have been to 0.5 mg/m^3 Ni.]

(vi) *Aircraft engine factory, Connecticut, USA*

Bernacki *et al.* (1978b) compared the employment histories of 42 men at an aircraft engine factory in the USA who had died of lung cancer with those of 84 age-matched men who had died of causes other than cancer. The proportion classified as nickel-exposed was identical (26%) among cases and controls. Atmospheric nickel concentrations in the past were believed to have been < 1 mg/m^3.

(*e*) *Other studies*

Several studies have been reported in which occupational histories of nasal cancer patients were sought by interview with patients or relatives, from medical or other records, or from death certificates. Acheson *et al.* (1981), in a study of 1602 cases diagnosed in England and Wales over a five-year period, found an excess (29 cases; SMR, 250 [95% CI, 167-359]) in furnace and foundry workers, which was partly (but not entirely) due to the inclusion of seven process workers from the INCO (Clydach) nickel refinery (see above). Hernberg *et al.* (1983) studied 287 cases diagnosed in Denmark, Finland or Sweden over a 3.5-year period. The association with exposure to nickel (12 cases, five matched controls among 167 matched case-control pairs who were interviewed; odds ratio, 2.4; 95% CI, 0.9-6.6) was not statistically significant. All except one of the nickel-exposed cases (a nickel refinery worker) had also been classified as having exposure to chromium (odds ratio, 2.7;

95% CI, 1.1-6.6), which was significantly associated with nasal cancer risk. Brinton *et al.* (1984) recorded exposure to nickel in only one (RR, 1.8; 95% CI, 0.1-27.6) of 160 cases and one of 290 controls in a hospital-based study between 1970 and 1980 in North Carolina and Virginia. Roush *et al.* (1980) examined exposure to nickel, cutting oils and wood dust in a case-control study based on all sinonasal cancer deaths in Connecticut in 1935-75. Job titles were obtained from deaths certificates and city directories and were classified according to estimated airborne exposures. Ten of 216 cases and 49 of 662 controls were classified as having been exposed to nickel (RR, 0.71; 95% CI, 0.4-1.5).

Gérin *et al.* (1984) reported significantly more frequent exposure to nickel among 246 Canadian lung cancer patients (29 exposed; odds ratio, 3.1; 95% CI, 1.9-5.0) than among patients with other cancers. All 29 cases had also been exposed to chromium, and 20 (69%) had been exposed to stainless-steel welding fumes. In a case-control study of 326 Danish laryngeal cancer patients, Olsen and Sabroe (1984) found a statistically significant association with exposure to nickel from alloys, battery chemicals and chemicals used in plastics production (RR, 1.7; 95% CI, 1.2-2.5; adjusted for age, tobacco and alcohol consumption and sex).

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Nickel, in the form of various alloys and compounds, has been in widespread commercial use for over 100 years. Several million workers worldwide are exposed to airborne fumes, dusts and mists containing nickel and its compounds. Exposures by inhalation, ingestion or skin contact occur in nickel and nickel alloy production plants as well as in welding, electroplating, grinding and cutting operations. Airborne nickel levels in excess of 1 mg/m^3 have been found in nickel refining, in the production of nickel alloys and nickel salts, and in grinding and cutting of stainless-steel. In these industries, modern control technologies have markedly reduced exposures in recent years. Few data are available to estimate the levels of past exposures to total airborne nickel, and the concentrations of individual nickel compounds were not measured.

Occupational exposure has been shown to give rise to elevated levels of nickel in blood, urine and body tissues, with inhalation as the main route of uptake. Non-occupational sources of nickel exposure include food, air and water, but the levels found are usually several orders of magnitude lower than those typically found in occupational situations.

Table 26. INCO Ontario (Canada) nickel refinery facilities – average nickel exposure levels and cancer risks in workers with 15 or more years since first exposure[a]

Plant	Department	Estimated airborne concentration (mg/m^3 Ni)					Duration in department							
							Ever				≥5 years			
							Lung cancer		Nasal cancer		Lung cancer		Nasal cancer	
		Metallic nickel	Oxidic nickel	Sulfidic nickel	Soluble nickel	Total nickel	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Coniston	Sinter	Negl.[b]	0.1–0.5	1–5	Negl.	1–5	8	292 (126–576)	0	–	6	492 (181–1073)	0	–
Copper Cliff	Sinter													
1948–54		Negl.	25–60	15–35	< 4	40–100	63	307 (238–396)	6	3617 (1327–7885)	33	789 (543–1109)	4	13 146 (3576–33 654)
1955–63		Negl.	5–25	3–15	< 2	8–40								
Port Colborne	Leaching, calcining, sintering													
1926–35		Negl.	20–40	10–20	< 3	30–80	72	239 (187–302)	19	7776 (4681–12 144)	38	366 (259–502)	15	18 750 (10 500–30 537)
1936–45		Negl.	3–15	2–10	< 3	5–25								
1946–58		Negl.	5–25	3–15	< 3	8–40								
	Electrolysis	< 0.5	< 0.2	< 0.5	< 0.3	< 1	19	88[d] (53–137)	0[c,d]	–	10[d,e]	89	0[c,d]	–

[a]From ICNCM (1990), estimated average airborne concentrations of nickel species and mortality from lung cancer and nasal cancer by department; standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]Negl., negligible exposure

[c]Two nasal cancer deaths occurred in men with > 20 years in electrolysis and only short exposure (three months and seven months) in leaching, calcining and sintering

[d]Never worked in leaching, calcining and sintering

[e]Workers with ≥10 years in electrolysis

Table 27. MOND/INCO (Clydach, South Wales, UK) nickel refinery – average nickel exposure levels and cancer risks in 'high-risk' departments in workers with 15 or more years since first exposure[a]

Department	Estimated airborne concentration (mg/m^3 Ni)[b]				Duration in department							
					Ever				≥5 years			
	Metallic nickel	Oxidic nickel	Sulfidic nickel	Soluble nickel	Lung cancer		Nasal cancer		Lung cancer		Nasal cancer	
					Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Furnaces, 1905–63	5.6	6.4	2.6	0.4	9	409	3	24 781	1	370	3	1000
Linear calciners, 1902–30; milling and grinding, 1902–36	5.3	18.8	6.8	0.8	16	725	7	44 509	12	1244	6	78 280
Copper plant, before 1937	–	13.1	0.4	1.1	17	317 (185–507)	5	13 912 (4507–32 415)	8	541 (233–1066)	2	14 541 (1759–52 493)
1938–60	–	0.4	0.01	0.01	–		–		–		–	
Hydrometallurgy 1902–79	0.5	0.9	0.05	1.3	7	196 (79–404)	4	18 779 (5108–48 074)	5	333 (108–776)	4	36 363 (9891–93 089)

[a]From ICNCM (1990); estimated average airborne concentrations of nickel species and mortality from lung cancer and nasal cancer by department. In each row, observations are restricted to men with < 1 year employment in other high-risk departments. Standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]The Working Group expressed reservations about the accuracy of these estimates, as discussed on p. 391.

Table 28. Falconbridge (Kristiansand, Norway) nickel refinery – average nickel exposure levels and cancer risks in workers with 15 or more years since first exposure[a]

Department	Estimated airborne concentration (mg/m^3 Ni)				Duration in department							
	Metallic nickel	Oxidic nickel	Sulfidic nickel	Soluble nickel	Ever				≥5 years			
					Lung cancer		Nasal cancer[b]		Lung cancer		Nasal cancer[b]	
					Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Calcining, roasting, smelting; never in electrolysis	0.3–1.3	5.0–10.0	0.3	Negl.[c]	14	225 (122–377)	5	–	8	254 (109–500)	5	–
Electrolysis; never in calcining, roasting smelting	0.3–1.3	0.3–1.3	Negl.–1.3	1.3–5.0	30	385 (259–549)	2	–	19	476 (287–744)	2	–

[a]From ICNCM (1990); estimated average airborne concentrations of nickel species and mortality from or incidence of lung cancer and nasal cancer by department; standardized mortality ratio (SMR) and 95% confidence interval (CI)

[b]Three deaths and four incident cases

[c]Negl., negligible exposure

4.2 Experimental carcinogenicity data

Metallic nickel and nickel alloys

Metallic nickel was tested by inhalation exposure in mice, rats and guinea-pigs, by intratracheal instillation in rats, by intramuscular injection in rats and hamsters, and by intrapleural, subcutaneous, intraperitoneal and intrarenal injection in rats. The studies by inhalation exposure were inadequate for an assessment of carcinogenicity. After intratracheal instillation, it produced significant numbers of squamous-cell carcinomas and adenocarcinomas of the lung. Intrapleural injections induced sarcomas. Subcutaneous administration of metallic nickel pellets induced sarcomas in rats, intramuscular injection of nickel powder induced sarcomas in rats and hamsters, and intraperitoneal injections induced carcinomas and sarcomas. No significant increase in the incidence of local kidney tumours was seen following intrarenal injection.

Nickel alloys were tested by intramuscular, intraperitoneal and intrarenal injection and by subcutaneous implantation of pellets in rats. A ferronickel alloy did not induce local tumours after intramuscular or intrarenal injection. Two powdered nickel alloys induced malignant tumours following intraperitoneal injection, and one nickel alloy induced sarcomas following subcutaneous implantation in pellets.

Nickel oxides and hydroxides

Nickel monoxide was tested by inhalation exposure in rats and hamsters, by intratracheal instillation in rats, by intramuscular administration in two strains of mice and two strains of rats, and by intrapleural, intraperitoneal and intrarenal injection in rats. The two studies by inhalation exposure in rats were inadequate for an assessment of carcinogenicity; lung tumours were not induced in the study in hamsters. Intratracheal instillation resulted in a significant incidence of lung carcinomas. Local sarcomas were induced at high incidence after intrapleural, intramuscular and intraperitoneal injection. No renal tumour was seen following intrarenal injection.

Two studies in rats in which *nickel trioxide* was injected intramuscularly or intracerebrally were inadequate for evaluation.

In a study in which *nickel hydroxide* was tested in three physical states by intramuscular injection in rats, local sarcomas were induced by dry gel and crystalline forms. Local sarcomas were induced in one study in which nickel hydroxide was tested by intramuscular injection in rats.

Nickel sulfides

Nickel subsulfide was tested by inhalation exposure and by intratracheal instillation in rats, by subcutaneous injection to mice and rats, by intramuscular admin-

istration to mice, rats, hamsters and rabbits, by intrapleural, intraperitoneal, intrarenal, intratesticular, intraocular and intra-articular administration in rats, by injection into retroperitoneal fat in rats, by implantation into rat heterotopic tracheal transplants and by administration to pregnant rats.

After exposure by inhalation, rats showed a significant increase in the incidence of benign and malignant lung tumours. Multiple intratracheal instillations resulted in malignant lung tumours (adenocarcinomas, squamous-cell carcinomas and mixed tumours).

A high incidence of local sarcomas was observed in rats after intrapleural administration. Subcutaneous injection induced sarcomas in mice and rhabdomyosarcomas and fibrous histiocytomas in rats. Nickel subsulfide has been shown consistently to induce local sarcomas following intramuscular administration, and dose-response relationships were demonstrated in rats and hamsters. The majority of the sarcomas induced were of myogenic origin, and the incidences of metastases were generally high. In rats, strain differences in tumour incidence and local tissue responses were seen. After intramuscular implantation of millipore diffusion chambers containing nickel subsulfide, a high incidence of local sarcomas was induced.

Mesotheliomas were included among the malignancies induced by intraperitoneal administration. Intrarenal injections resulted in a dose-related increase in the incidence of renal-cell neoplasms. A high incidence of sarcomas (including some rhabdomyosarcomas) was seen after intratesticular injection, and a high incidence of eye neoplasms (including retinoblastomas, melanomas and gliomas) after intraocular injection. Intra-articular injection induced sarcomas (including rhabdomyosarcomas and fibrous histiocytomas), and injection into retroperitoneal fat induced mainly fibrous histiocytomas. Implantation of pellets containing nickel subsulfide into rat heterotopic tracheal transplants induced both carcinomas and sarcomas; in the group given the highest dose, sarcomas predominated. The study in which pregnant rats were injected with nickel subsulfide early in gestation was inadequate for evaluation.

Nickel disulfide was tested by intramuscular and intrarenal injection in rats. High incidences of local tumours were induced.

Nickel monosulfide was tested by intramuscular and intrarenal injection in rats. The crystalline form induced local tumours, but the amorphous form did not.

Nickel ferrosulfide matte induced local sarcomas after administration by intramuscular injection in rats.

Nickel salts

Nickel sulfate was tested for carcinogenicity by intramuscular and intraperitoneal injection in rats. Repeated intramuscular injections did not induce local

tumours; however, intraperitoneal injections induced malignant tumours in the peritoneal cavity.

Nickel chloride was tested by repeated intraperitoneal injections in rats, inducing malignant tumours in the peritoneal cavity.

Nickel acetate was tested by intraperitoneal injection in mice and rats. After repeated intraperitoneal injections in rats, malignant tumours were induced in the peritoneal cavity. In strain A mice, lung adenocarcinomas were induced in one study and an increased incidence of pulmonary adenomas in two studies.

Studies in rats in which *nickel carbonate* was tested for carcinogenicity by intraperitoneal administration and *nickel fluoride* and *nickel chromate* by intramuscular injection could not be evaluated.

Other forms of nickel

Nickel carbonyl was tested for carcinogenicity by inhalation exposure and intravenous injection in rats. After inhalation exposure, a few lung carcinomas were observed two years after the initial treatment. Intravenous injection induced an increase in the overall incidence of neoplasms, which were located in several organs.

Nickelocene induced some local tumours in rats and hamsters following intramuscular injection.

One sample of *dust collected in nickel refineries*, containing nickel subsulfide and various proportions of nickel monoxide and nickel sulfate, induced sarcomas in mice and rats following intramuscular injection. Intraperitoneal administration of two samples of dust, containing unspecified nickel sulfides and various proportions of nickel oxide, soluble nickel and metallic nickel, induced sarcomas in rats. In a study in which hamsters were given prolonged exposure to a *nickel-enriched fly ash* by inhalation, the incidence of tumours was not increased.

Intramuscular administration to rats of *nickel sulfarsenide*, two *nickel arsenides*, *nickel antimonide*, *nickel telluride* and two *nickel selenides* induced significant increases in the incidence of local sarcomas, whereas administration of *nickel monoarsenide* and *nickel titanate* did not. None of these compounds increased the incidence of renal-cell tumours in rats after intrarenal injection.

4.3 Human carcinogenicity data

Increased risks for lung and nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies in Canada, Norway (Kristiansand) and the UK (Clydach), with exposures in electrolytic refining in a study in Norway, and with exposures during leaching of nickel-copper oxides in acidic solution (copper plant) and extraction of nickel salts from concentrated solution (hydrometallurgy) in the UK (see Table 26).

The substantial excess risk for lung and nasal cancer among Clydach hydrometallurgy workers seems likely to be due, at least partly, to their exposure to 'soluble nickel'. Their estimated exposures to other types of nickel (metallic, sulfidic and oxidic) were up to an order of magnitude lower than those in several other areas of the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. Similarly, high risks for lung and nasal cancers were observed among electrolysis workers at Kristiansand. These men were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulfate was the only or predominant soluble nickel species present in these areas.

The highest risks for lung and nasal cancers were observed among calcining workers, who were heavily exposed to both sulfidic and oxidic nickel. A high lung cancer rate was also seen among nickel plant cleaners at Clydach, who were heavily exposed to these insoluble compounds, with little or no exposure to soluble nickel. The separate effects of oxides and sulfides cannot be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in calcining furnaces and nickel plant cleaners were also exposed to high levels of metallic nickel.

Among hard-rock sulfide nickel ore miners in Canada, there was some increase in lung cancer risk, but exposure to other substances could not be excluded. In studies of open-cast miners of silicate-oxide nickel ores in the USA and in New Caledonia, no significant increase in risk was seen, but the numbers of persons studied were small and the levels of exposure were reported to be low.

No significant excess of respiratory tract cancer was observed in three studies of workers in high-nickel alloy manufacture or in a small study of users of metallic nickel powder. No increase in risk for lung cancer was observed in one small group of nickel electroplaters in the UK with no exposure to chromium.

In a case-control study, an elevated risk for lung cancer was found among persons exposed to nickel together with chromium-containing materials.

The results of epidemiological studies of stainless-steel welders are consistent with the finding of excess mortality from lung cancer among other workers exposed to nickel compounds, but they do not contribute independently to the evaluation of nickel since welders are also exposed to other compounds. (See also the monograph on welding.)

4.4 Other relevant data

Nickel and nickel compounds are absorbed from the respiratory tract, and to a smaller extent from the gastrointestinal tract, depending on dissolution and cellular uptake. Absorbed nickel is excreted predominantly in the urine. Nickel tends to persist in the lungs of humans and of experimental animals, and increased concen-

trations are seen notably in workers after inhalation of nickel. The nasal mucosa may retain nickel for many years.

Nickel carbonyl is the most acutely toxic nickel compound and causes severe damage to the respiratory system in experimental animals and in humans. Nickel causes contact dermatitis in humans. In experimental animals, adverse effects have also been documented in the respiratory system and in the kidney.

In four studies, the frequency of sister chromatid exchange did not appear to be increased in peripheral blood lymphocytes of nickel workers exposed during various processes. Enhanced frequencies of chromosomal gaps and/or anomalies were observed in single studies in peripheral blood lymphocytes of employees engaged in: (i) crushing, roasting and smelting (exposure mainly to nickel oxide and nickel subusulfide); (ii) electrolysis (exposure mainly to nickel chloride and nickel sulfate); and (iii) electroplating (exposure to nickel and chromium compounds). Enhanced frequencies were also seen in lymphocytes from retired workers who had previously been exposed in crushing, roasting and smelting and/or electrolysis.

Some nickel compounds have adverse effects on reproduction and prenatal development in rodents. Decreased fertility, reduction in the number of pups per litter and birth weight per pup, and a pattern of anomalies, including eye malformations, cystic lungs, hydronephrosis, cleft palate and skeletal deformities, have been demonstrated.

In one study, metallic nickel did not induce chromosomal aberrations in cultured human cells, but it transformed animal cells *in vitro*. Nickel oxides induced anchorage-independent growth in human cells *in vitro* and transformed cultured rodent cells; they did not induce chromosomal aberrations in cultured human cells in one study.

Crystalline nickel subsulfide induced anchorage-independent growth and increased the frequency of sister chromatid exchange but did not cause gene mutation in human cells *in vitro*. Crystalline nickel sulfide and subsulfide induced cell transformation, gene mutation and DNA damage in cultured mammalian cells; the sulfide also induced chromosomal aberrations and sister chromatid exchange. Amorphous nickel sulfide did not transform or produce DNA damage in cultured mammalian cells. In one study, crystalline nickel sulfide and crystalline nickel subsulfide produced DNA damage in *Paramoecium*.

Nickel chloride and nickel nitrate were inactive in assays *in vivo* for induction of dominant lethal mutation and micronuclei, and nickel sulfate did not induce chromosomal aberrations in bone-marrow cells; however, nickel chloride induced chromosomal aberrations in Chinese hamster and mouse bone-marrow cells.

Soluble nickel compounds were generally active in the assays of human and animal cells *in vitro* in which they were tested.

Nickel sulfate and nickel acetate induced anchorage-independent growth in human cells *in vitro*. Nickel sulfate increased the frequency of chromosomal aberrations in human cells, and nickel sulfate and nickel chloride increased the frequency of sister chromatid exchange. Nickel sulfate did not induce single-strand DNA breaks in human cells. Nickel sulfate and nickel chloride transformed cultured mammalian cells. Chromosomal aberrations were induced in mammalian cells by nickel chloride, nickel sulfate and nickel acetate, and sister chromatid exchange was induced by nickel chloride and nickel sulfate. Nickel chloride and nickel sulfate also induced gene mutation, and nickel chloride caused DNA damage in mammalian cells. In one study, nickel sulfate inhibited intercellular communication in cultured mammalian cells.

Nickel sulfate induced aneuploidy and gene mutation in a single study in *Drosophila*; nickel chloride and nickel nitrate did not cause gene mutation. Nickel chloride induced gene mutation and recombination in yeast.

In single studies, nickel acetate produced DNA damage in bacteria, while nickel nitrate did not; the results obtained with nickel chloride were inconclusive. In bacteria, neither nickel acetate, sulfate, chloride nor nitrate induced gene mutation.

Nickel carbonate induced DNA damage in rat kidney *in vivo*. Crystalline nickel subselenide transformed cultured mammalian cells, and nickel potassium cyanide increased the frequency of chromosomal aberrations. Nickelocene did not induce bacterial gene mutation. DNA damage was induced in calf thymus nucleohistone by nickel[III]-tetraglycine complexes.

4.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of nickel sulfate, and of the combinations of nickel sulfides and oxides encountered in the nickel refining industry.

There is *inadequate evidence* in humans for the carcinogenicity of metallic nickel and nickel alloys.

There is *sufficient evidence* in experimental animals for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides and crystalline nickel sulfides.

There is *limited evidence* in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonide, nickel selenides and nickel telluride.

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[1]For descriptions of the italicized terms, see Preamble, pp. 33–37.

There is *inadequate evidence* in experimental animals for the carcinogenicity of nickel trioxide, amorphous nickel sulfide and nickel titanate.

The Working Group made the overall evaluation on nickel compounds as a group on the basis of the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and several types of other relevant data, supported by the underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells.

Overall evaluation

Nickel compounds *are carcinogenic to humans* (Group 1).

Metallic nickel *is possibly carcinogenic to humans* (Group 2B).

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NICKEL OCCUPATIONAL EXPOSURE

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE (LED OR HID)	REFERENCE
S	SLH	SCE, HUMAN LYMPHOCYTES IN VIVO	–	0	0.1400	WAKSVIK ET AL., 1984[1]
S	SLH	SCE, HUMAN LYMPHOCYTES IN VIVO	–	0	0.0680	WAKSVIK & BOYSEN, 1982[2]
S	SLH	SCE, HUMAN LYMPHOCYTES IN VIVO	–	0	0.0280	WAKSVIK & BOYSEN, 1982[3]
S	SLH	SCE, HUMAN LYMPHOCYTES IN VIVO	(+)	0	0.0140	DENG ET AL., 1983[4]
S	SLH	SCE, HUMAN LYMPHOCYTES IN VIVO	–	0	0.0000	DECHENG ET AL., 1987[5]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES IN VIVO	+	0	0.1400	WAKSVIK ET AL., 1984[1]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES IN VIVO	+	0	0.0680	WAKSVIK & BOYSEN, 1982[2]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES IN VIVO	+	0	0.0280	WAKSVIK & BOYSEN, 1982[3]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES IN VIVO	+	0	0.0140	DENG ET AL., 1983[4]
C	CLH	CHROM ABERR, HUMAN LYMPHOCYTES IN VIVO	–	0	0.0000	DECHENG ET AL., 1987[5]

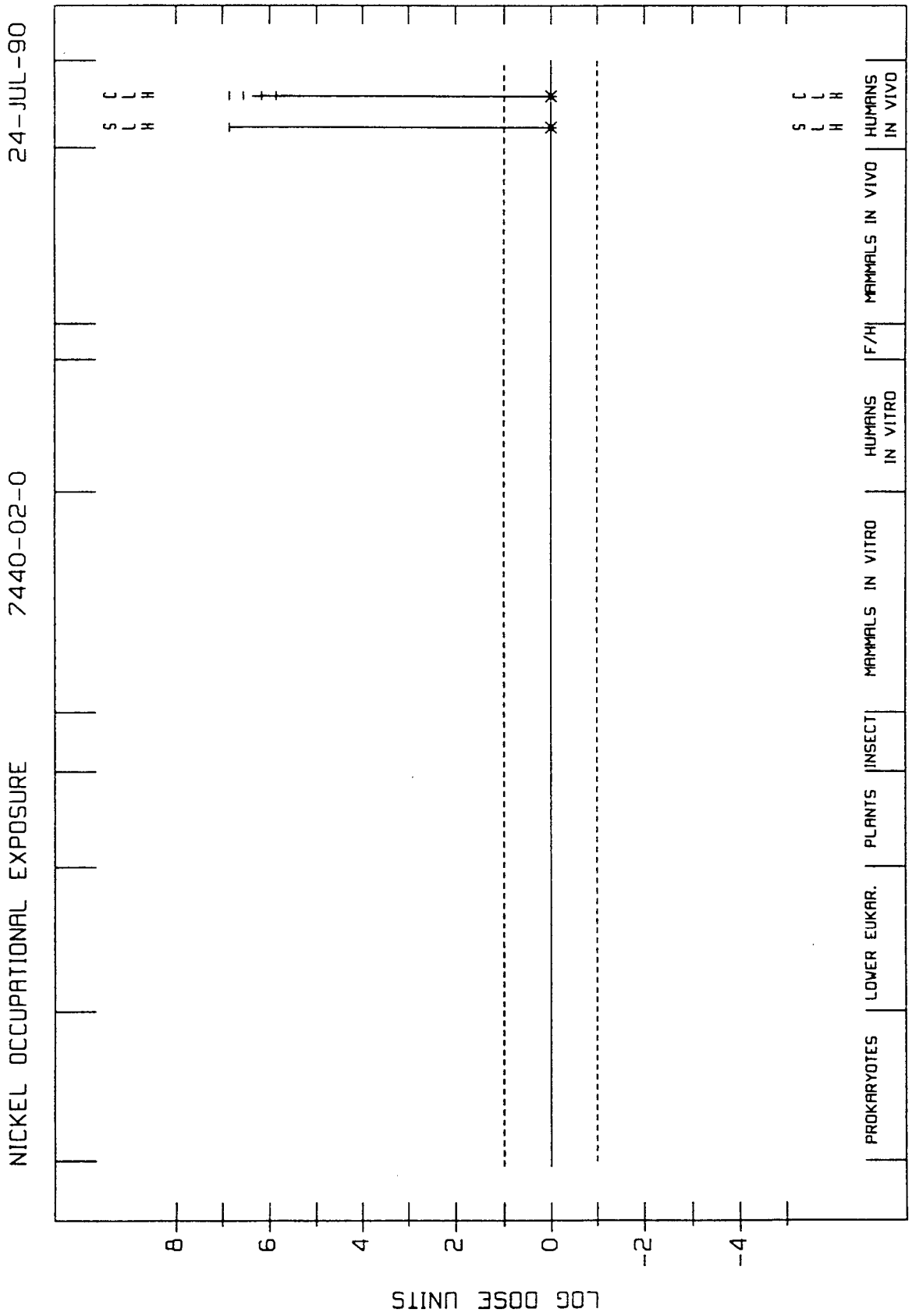
[1] NiO and $Ni_3S_2/NiCl_2$, $NiSO_4$ (crushing, roasting, smelting and/or electrolysis)

[2] NiO and Ni_3S_2 (crushing, roasting, smelting)

[3] $NiCl_2$ and $NiSO_4$ (electrolysis)

[4] Ni and chromium (electroplating)

[5] $Ni(CO)_4$ (production of nickel carbonyl)


NICKEL OCCUPATIONAL EXPOSURE
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24-JUL-90
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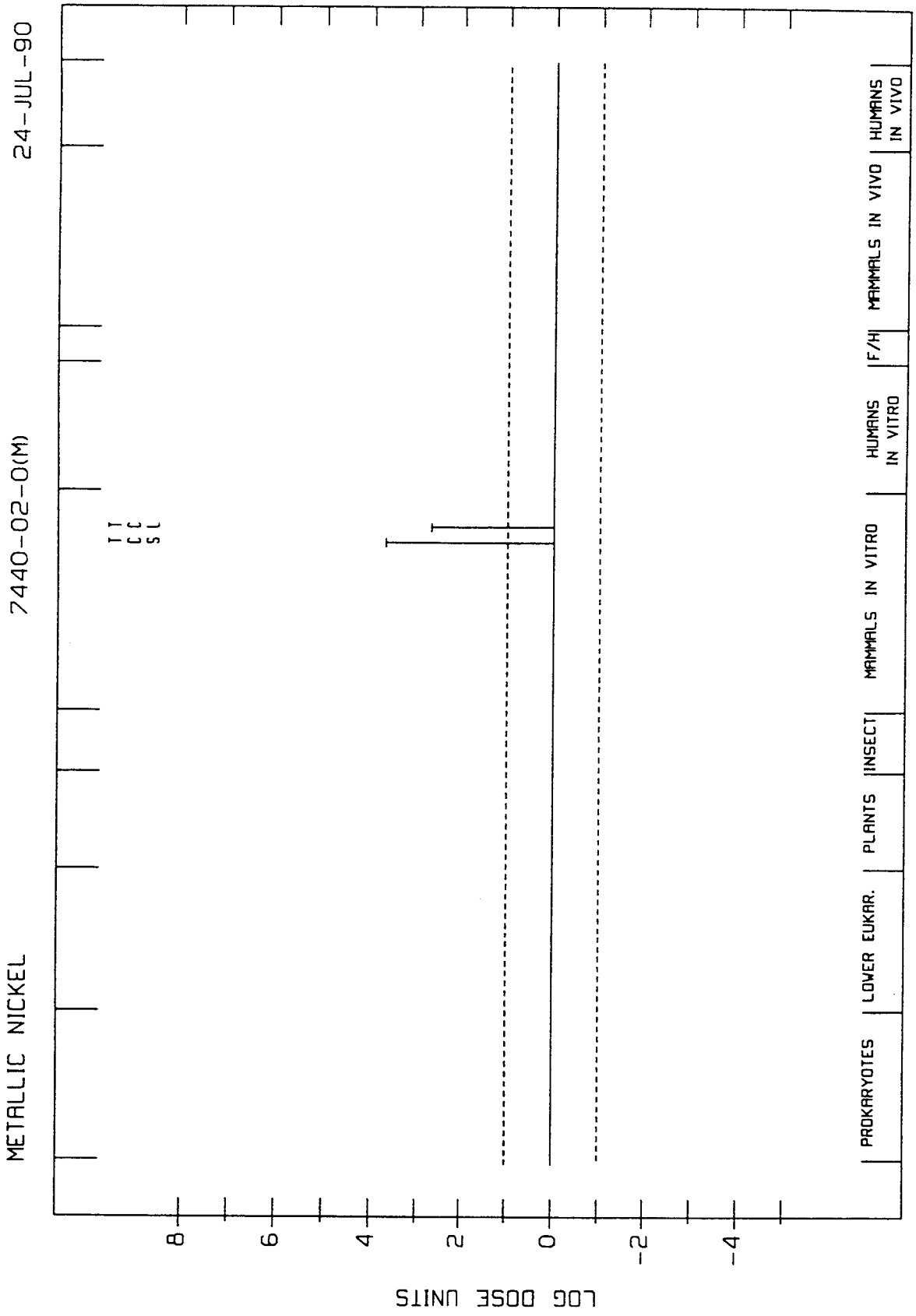
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/H
MAMMALS IN VIVO
HUMANS IN VIVO

METALLIC NICKEL

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	20.0000	COSTA ET AL., 1981b
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	+	0	200.0000	HANSEN & STERN, 1984
C	CHL	CHROM ABERR, HUMAN LYMPHOCYTES IN VITRO	−	0	0.0000	PATON & ALLISON, 1972

[1]Doses are given as concentrations of the element, not the concentration of the compound.


METALLIC NICKEL
7440-02-0(M)
24-JUL-90
I I
C C
S L
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
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HUMANS IN VIVO
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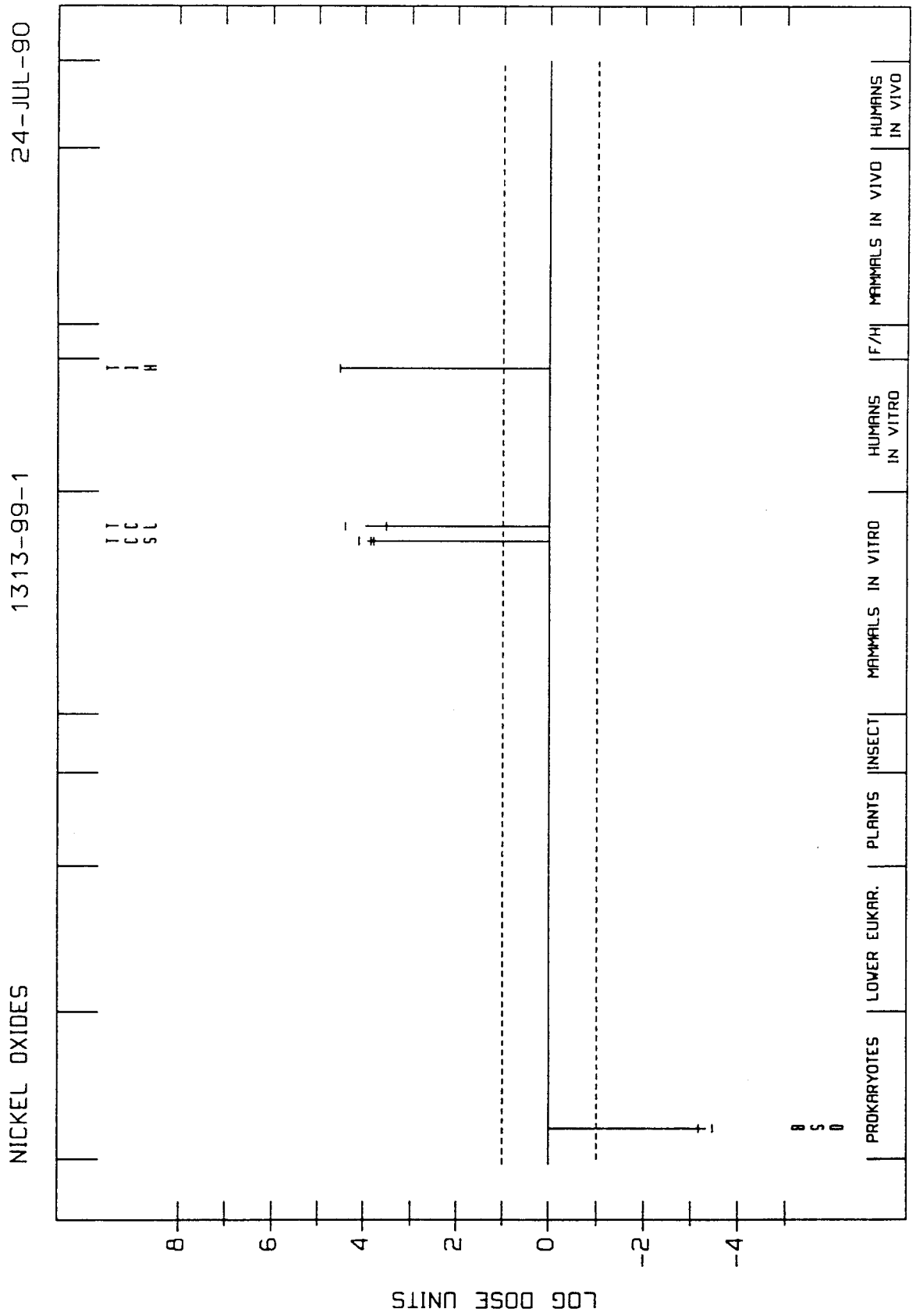
LOG DOSE UNITS

NICKEL OXIDES

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
D	BSD	B. SUBTILIS REC, DIFFERENTIAL TOXICITY[2]	–	0	1475.0000	KANEMATSU ET AL., 1980
D	BSD	B. SUBTILIS REC, DIFFERENTIAL TOXICITY[3]	–	0	2950.0000	KANEMATSU ET AL., 1980
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY[2]	+	0	16.0000	COSTA ET AL., 1981b
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY[3]	+	0	14.0000	COSTA ET AL., 1981b
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY[3]	+	0	7.9000	SUNDERMAN ET AL., 1987
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES[2]	+	0	30.0000	HANSEN & STERN, 1983
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES[3]	+	0	4.0000	HANSEN & STERN, 1983
C	CHL	CHROM ABERR, HUMAN LYMPHOCYTES IN VITRO[3]	–	0	0.0000	PATON & ALLISON, 1972
T	TIH	CELL TRANSFORMATION, HUMAN CELLS IN VITRO[3]	+	0	3.0000	BIEDERMANN & LANDOLPH, 1987

[1]Doses are given as concentrations of the element, not the concentration of the compound.
[2]Nickel trioxide
[3]Nickel monoxide


NICKEL OXIDES
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24-JUL-90
LOG DOSE UNITS
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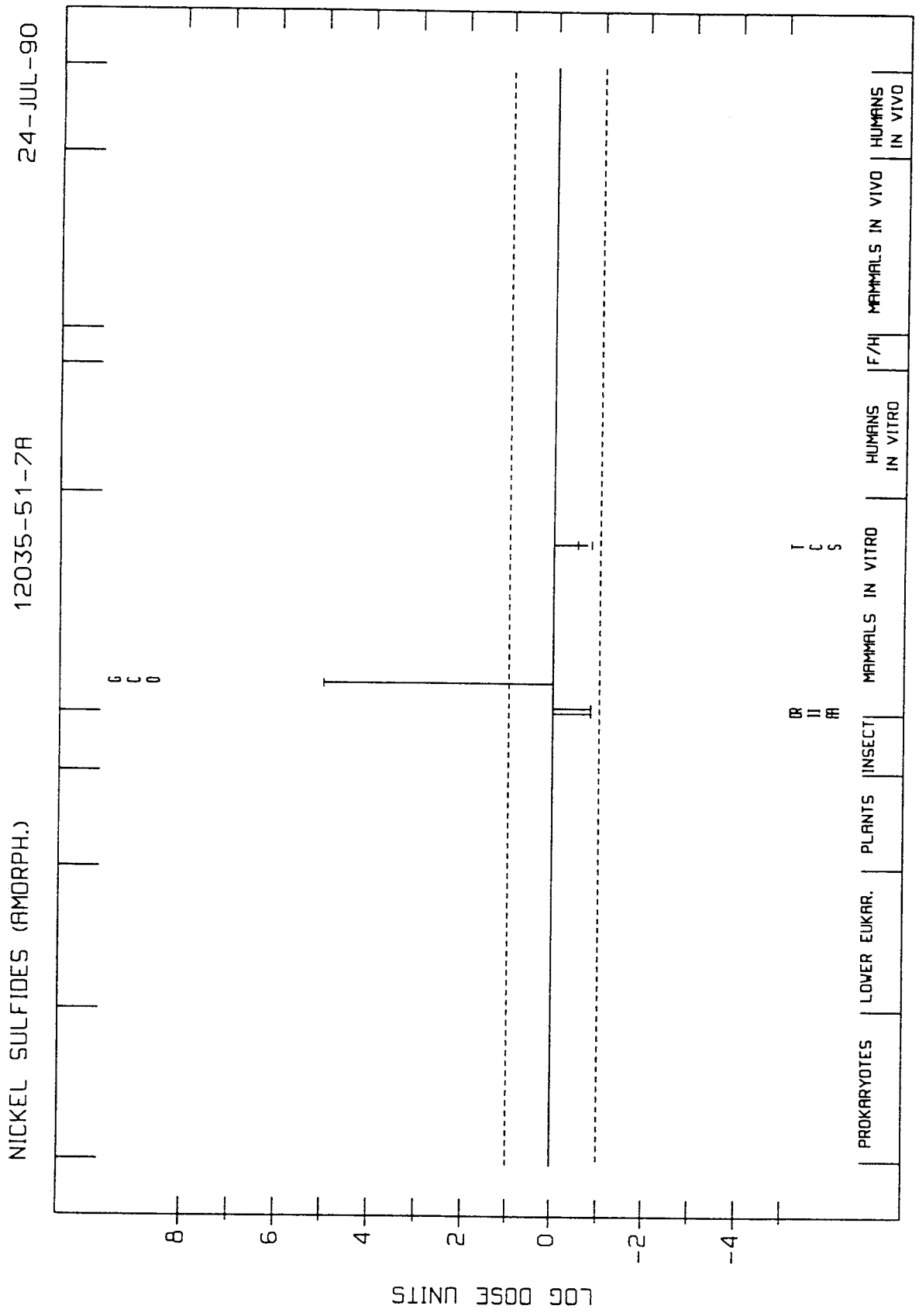
2
0
-2
-4
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/HI
MAMMALS IN VIVO
HUMANS IN VIVO

NICKEL SULFIDES (AMORPH.)

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	-	0	6.5000	COSTA ET AL., 1982
D	RIA	OTHER DNA REPAIR, ANIMAL CELLS IN VITRO	-	0	6.5000	ROBISON ET AL., 1983
G	GCO	MUTATION, CHO CELLS IN VITRO	(+)	0	1.0000	COSTA ET AL., 1980
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	-	0	3.2500	COSTA ET AL., 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	-	0	6.5000	COSTA & MOLLENHAUER, 1980a
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	-	0	6.5000	COSTA ET AL., 1982

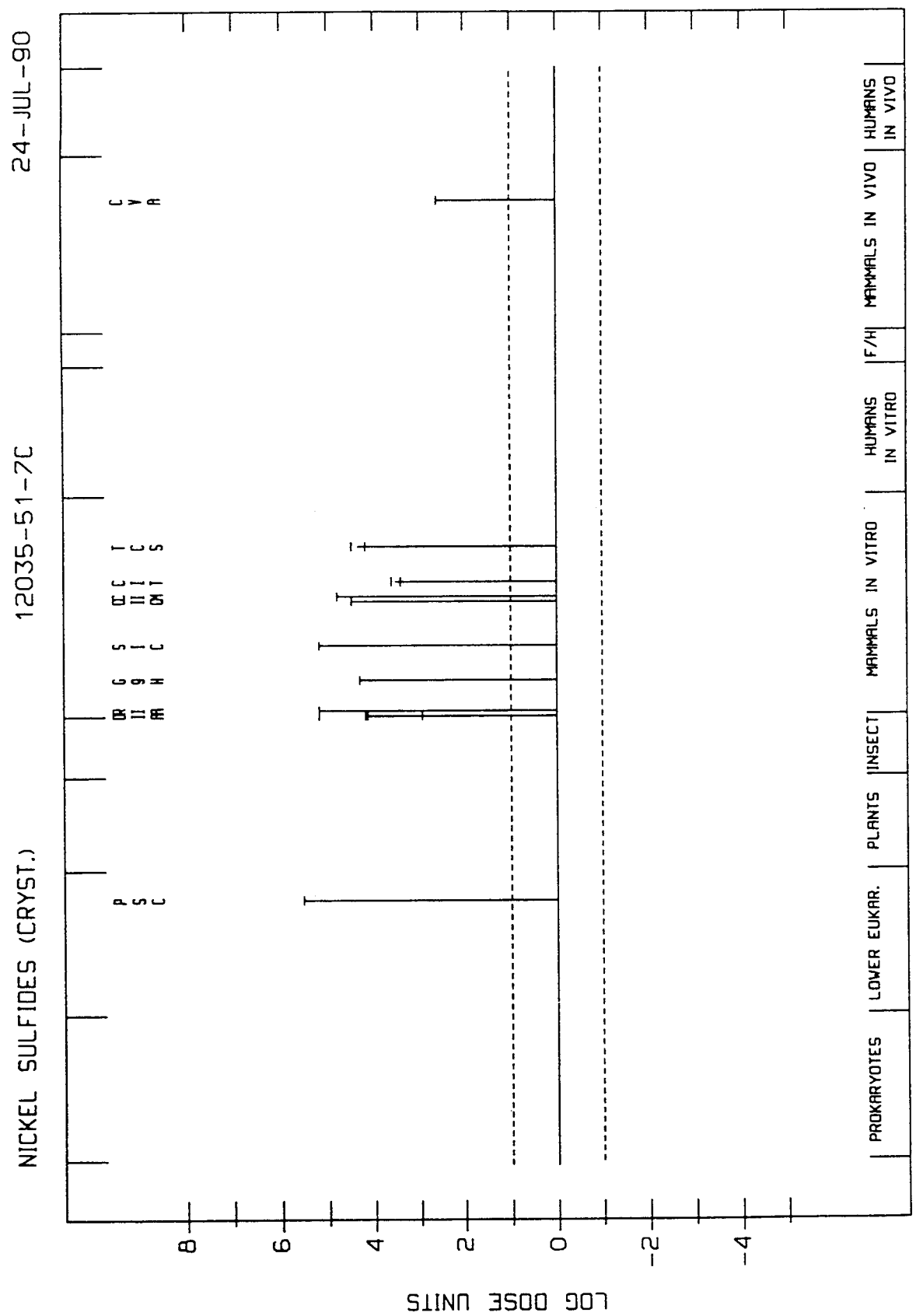
[1]Doses are given as concentrations of the element, not the concentration of the compound.


NICKEL SULFIDES (AMORPH.)
12035-51-7A
24-JUL-90
LOG DOSE UNITS
8
6
4
2
0
-2
-4
GCO
ORAL
INCS
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/H
MAMMALS IN VIVO
HUMANS IN VIVO

NICKEL SULFIDES (CRYST.)

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
C	PSC	PARAMECIUM SPECIES, CHROM ABERR	+	0	0.3000	SMITH-SONNEBORN ET AL., 1983
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	(+)	0	114.0000	SINA ET AL., 1983
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	+	0	6.5000	COSTA ET AL., 1982
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	+	0	0:6500	ROBISON & COSTA, 1982
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	+	0	6.5000	PATIERNO & COSTA, 1985
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	+	0	7.3000	ROBINSON ET AL., 1982
D	RIA	OTHER DNA REPAIR, ANIMAL CELLS IN VITRO	+	0	0.6500	ROBISON ET AL., 1983
G	G9H	MUTATION, CHL V79 CELLS, HPRT	+	0	4.9000	CHRISTIE ET AL., 1990
S	SIC	SCE, CHINESE HAMSTER CELLS IN VITRO	+	0	0.6500	SEN & COSTA, 1986
C	CIC	CHROM ABERR, CHINESE HAMSTER CELLS IN VITRO	+	0	3.2000	SEN & COSTA, 1985
C	CIM	CHROM ABERR, MOUSE CELLS IN VITRO	+	0	1.6000	SEN ET AL., 1987
C	CIT	CHROM ABERR, TRANSFORMED CELLS IN VITRO	+	0	38.0000	UMEDA & NISHIMURA, 1979
C	CIT	CHROM ABERR, TRANSFORMED CELLS IN VITRO	+	0	24.0000	NISHIMURA & UMEDA, 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	6.5000	COSTA ET AL., 1982
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	3.2500	COSTA & MOLLENHAUER, 1980c
C	CVA	CHROM ABERR, OTHER ANIMAL CELLS IN VIVO	+	0	250.0000	CHRISTIE ET AL., 1988

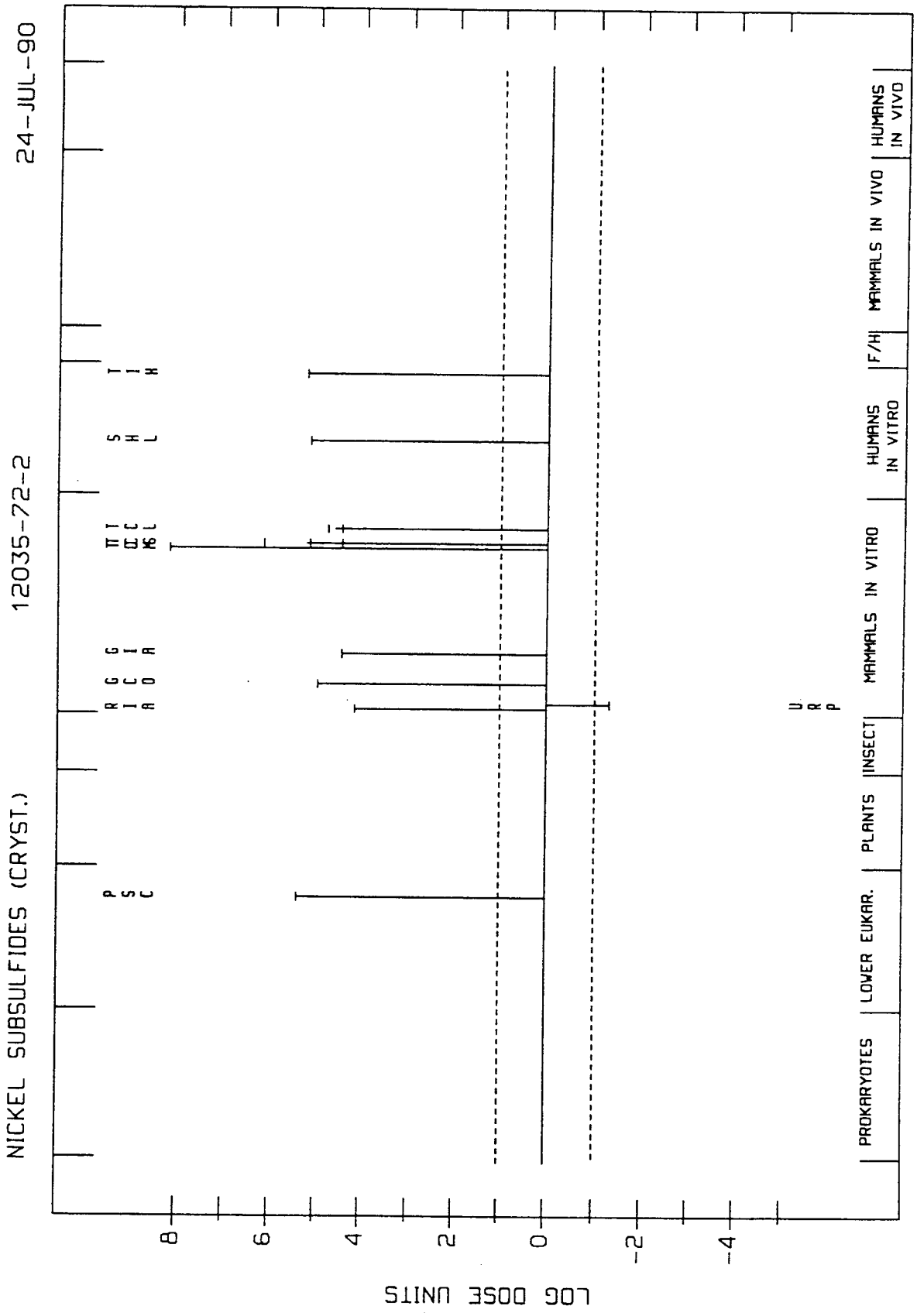
[1]Doses are given as concentrations of the element, not the contration of the compound.


NICKEL SULFIDES (CRYST.)
12035-51-7C
24-JUL-90
LOG DOSE UNITS
8
6
4
2
0
-2
-4
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/H
MAMMALS IN VIVO
HUMANS IN VIVO

NICKEL SUBSULFIDES

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
C	PSC	PARAMECIUM SPECIES, CHROM ABERR	+	0	0.4000	SMITH-SONNEBORN ET AL., 1983
D	RIA	OTHER DNA REPAIR, ANIMAL CELLS IN VITRO	+	0	7.3000	ROBISON ET AL., 1983
D	URP	UDS, RAT PRIMARY HEPATOCYTES	–	0	20.0000	SWIERENGA & MCLEAN, 1985
G	GCO	MUTATION, CHO CELLS IN VITRO	(+)	0	1.1000	COSTA ET AL., 1980
G	GIA	MUTATION, OTHER ANIMAL CELLS IN VITRO	+	0	3.7000	SWIERENGA & MCLEAN, 1985
T	TCM	CELL TRANSFORMATION, C3H10T1/2 CELLS	+	0	0.0007	SAXHOLM ET AL., 1981
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	0.7300	DIPAOLO & CASTO, 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	0.0730	COSTA ET AL., 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	0.7300	COSTA & MOLLENHAUER, 1980a
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	3.7000	COSTA & MOLLENHAUER, 1980c
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	+	0	3.7000	HANSEN & STERN, 1983
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	+	0	1.8000	SWIERENGA ET AL., 1989
G	GIH	MUTATION, HUMAN CELLS IN VITRO	–	0	0.6000	BIEDERMANN & LANDOLPH, 1987
S	SHL	SCE, HUMAN LYMPHOCYTES IN VITRO	+	0	0.7300	SAXHOLM ET AL., 1981
T	TIH	CELL TRANSFORMATION, HUMAN CELLS IN VITRO	+	0	0.6000	BIEDERMANN & LANDOLPH, 1987

[1]Doses are given as concentrations of the element, not the concentration of the compound.


NICKEL SUBSULFIDES (CRYST.)
12035-72-2
24-JUL-90
LOG DOSE UNITS
8
6
4
2
0
-2
-4
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/H
MAMMALS IN VIVO
HUMANS IN VIVO

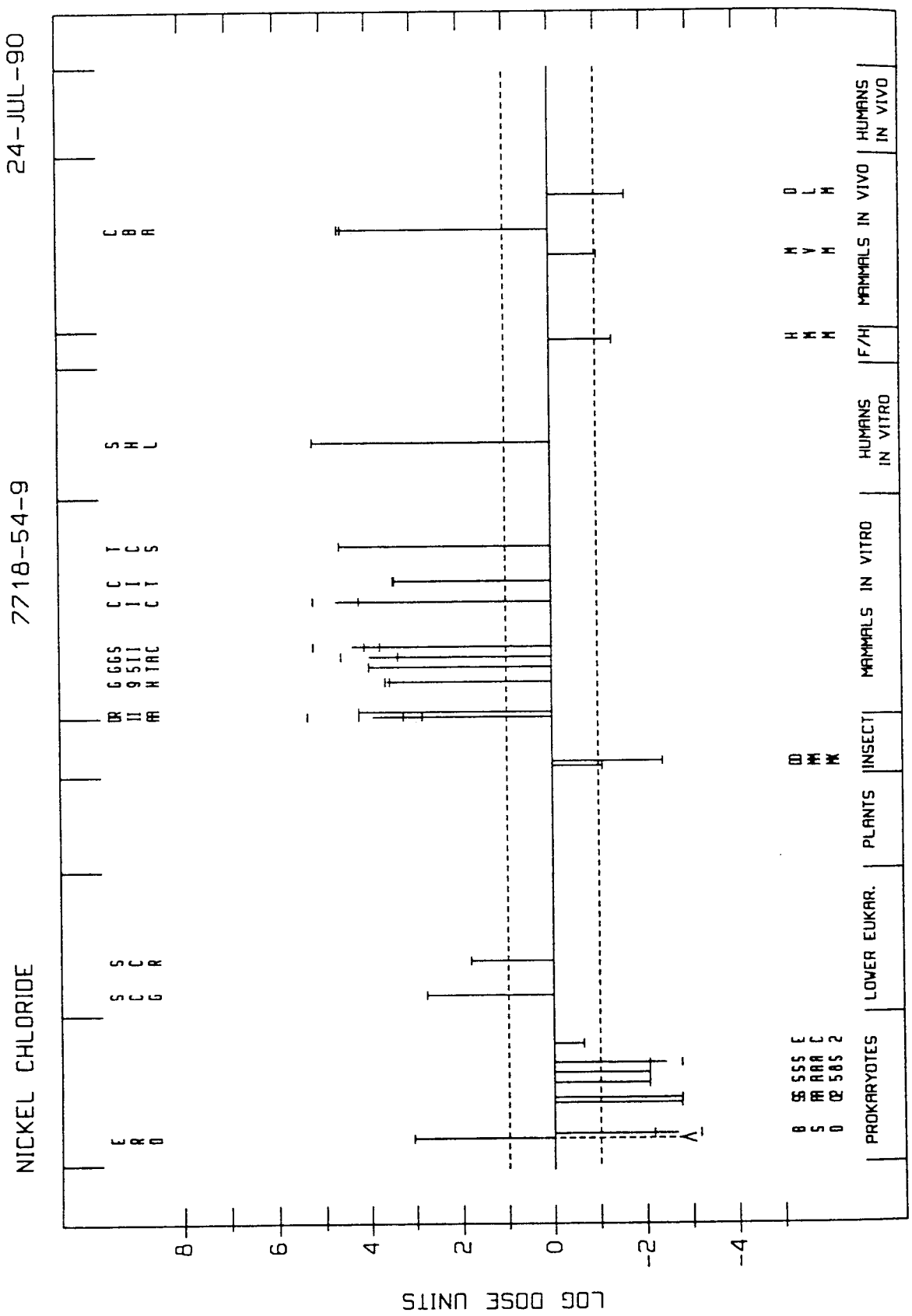
NICKEL CHLORIDE

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
D	ERD	E. COLI REC, DIFFERENTIAL TOXICITY	–	–	567.0000	DE FLORA ET AL., 1984a
D	ERD	E. COLI REC, DIFFERENTIAL TOXICITY	+	0	90.0000	TWEATS ET AL., 1981
D	ERD	E. COLI REC, DIFFERENTIAL TOXICITY	–	0	0.0100	DUBINS & LA VELLE, 1986
D	BSD	B. SUBTILIS REC, DIFFERENTIAL TOXICITY	–	0	1475.0000	KANEMATSU ET AL., 1980
D	BSD	B. SUBTILIS REC, DIFFERENTIAL TOXICITY	–	0	147.5000	NISHIOKA, 1975
G	SA0	S. TYPHIMURIUM TA100, REVERSE MUTATION	–	0	587.0000	TSO & FUNG, 1981
G	SA0	S. TYPHIMURIUM TA100, REVERSE MUTATION	–	0	0.0000	ARLAUSKAS ET AL., 1985
G	SA0	S. TYPHIMURIUM TA100, REVERSE MUTATION	–	–	0.0000	DE FLORA ET AL., 1984a
G	SA2	S. TYPHIMURIUM TA102, REVERSE MUTATION	–	0	590.0000	BIGGART & COSTA, 1986
G	SA5	S. TYPHIMURIUM TA1535, REVERSE MUTATION	–	0	0.0000	ARLAUSKAS ET AL., 1985
G	SA5	S. TYPHIMURIUM TA1535, REVERSE MUTATION	–	0	118.0000	BIGGART & COSTA, 1986
G	SA5	S. TYPHIMURIUM TA1535, REVERSE MUTATION	–	–	0.0000	DE FLORA ET AL., 1984a
G	SA7	S. TYPHIMURIUM TA1537, REVERSE MUTATION	–	0	0.0000	ARLAUSKAS ET AL., 1985
G	SA7	S. TYPHIMURIUM TA1537, REVERSE MUTATION	–	–	0.0000	DE FLORA ET AL., 1984a
G	SA8	S. TYPHIMURIUM TA1538, REVERSE MUTATION	–	0	0.0000	ARLAUSKAS ET AL., 1985
G	SA8	S. TYPHIMURIUM TA1538, REVERSE MUTATION	–	0	118.0000	BIGGART & COSTA, 1986
G	SA8	S. TYPHIMURIUM TA1538, REVERSE MUTATION	–	–	0.0000	DE FLORA ET AL., 1984a
G	SA9	S. TYPHIMURIUM TA98, REVERSE MUTATION	–	0	0.0000	ARLAUSKAS ET AL., 1985
G	SA9	S. TYPHIMURIUM TA98, REVERSE MUTATION	–	–	0.0000	DE FLORA ET AL., 1984a
G	SAS	S. TYPHIMURIUM (OTHER), REVERSE MUTATION	–	0	590.0000	TSO & FUNG, 1981
G	SAS	S. TYPHIMURIUM (OTHER), REVERSE MUTATION	–	0	118.0000	BIGGART & COSTA, 1986
G	SAS	S. TYPHIMURIUM (OTHER), REVERSE MUTATION	–	–	0.0000	DE FLORA ET AL., 1984a
G	EC2	E. COLI WP2, REVERSE MUTATION	–	0	4.5000	GREEN ET AL., 1976
R	SCG	S. CEREVISIAE, GENE CONVERSION	+	0	176.0000	FUKUNAGA ET AL., 1982
G	SCR	S. CEREVISIAE, REVERSE MUTATION	+	0	1535.0000	EGILSSON ET AL., 1979
G	DMM	D. MELANOGASTER, SOMATIC MUTAT/RECOMB	–	0	12.0000	RASMUSON, 1985
G	DMX	D. MELANOGASTER, SEX-LINKED RECESSIVES	–	0	248.0000	VOGEL, 1976
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	+	0	0.4500	ROBISON & COSTA, 1982
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	+	0	150.0000	PATIERNO & COSTA, 1985
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	+	0	5.9000	ROBISON ET AL., 1982
D	DIA	STRAND BREAKS/X-LINKS, ANIMAL CELLS IN VITRO	+	0	59.0000	ROBISON ET AL., 1984
D	RIA	OTHER DNA REPAIR, ANIMAL CELLS IN VITRO	+	0	5.9000	ROBISON ET AL., 1983
G	GCO	MUTATION, CHO CELLS IN VITRO	(+)	0	0.0000	HSIE ET AL., 1979
G	G9H	MUTATION, CHL V79 CELLS, HPRT	(+)	0	23.0000	MIYAKI ET AL., 1979
G	G9H	MUTATION, CHL V79 CELLS, HPRT	+	0	29.5000	HARTWIG & BEYERSMANN, 1989

NICKEL CHLORIDE

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
G	G5T	MUTATION, L5178Y CELLS, TK LOCUS	+	0	10.0000	AMACHER & PAILLET, 1980
G	GIA	MUTATION, OTHER ANIMAL CELLS IN VITRO	+	0	2.4000	BIGGART & MURPHY, 1988
G	GIA	MUTATION, OTHER ANIMAL CELLS IN VITRO	+	0	45.0000	SWIERENGA & MCLEAN, 1985
S	SIC	SCE, CHINESE HAMSTER CELLS IN VITRO	+	0	8.0000	OHNO ET AL., 1982
S	SIC	SCE, CHINESE HAMSTER CELLS IN VITRO	+	0	0.6000	SEN & COSTA, 1986
S	SIC	SCE, CHINESE HAMSTER CELLS IN VITRO	+	0	17.7000	HARTWIG & BEYERSMANN, 1989
C	CIC	CHROM ABERR, CHINESE HAMSTER CELLS IN VITRO	+	0	0.6000	SEN & COSTA, 1985
C	CIC	CHROM ABERR, CHINESE HAMSTER CELLS IN VITRO	+	0	6.0000	SEN ET AL., 1987
C	CIT	CHROM ABERR, TRANSFORMED CELLS IN VITRO	(+)	0	38.0000	UMEDA & NISHIMURA, 1979
C	CIT	CHROM ABERR, TRANSFORMED CELLS IN VITRO	+	0	35.0000	NISHIMURA & UMEDA, 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	2.2500	ZHANG & BARRETT, 1988
D	DIH	STRAND BREAKS/X-LINKS, HUMAN CELLS IN VITRO	?	0	3.0000	MCLEAN ET AL., 1982
S	SHL	SCE, HUMAN LYMPHOCYTES IN VITRO	+	0	0.6000	NEWMAN ET AL., 1982
H	HMM	HOST-MEDIATED ASSAY, MICROBIAL CELLS	−	0	23.0000	BUSELMAIER ET AL., 1972
M	MVM	MICRONUCLEUS TEST, MICE IN VIVO	−	0	11.000	DEKNUDT & LEONARD, 1982
C	CBA	CHROM ABERR, ANIMAL BONE MARROW IN VIVO	+	0	2.3000	CHORVATOVICOVA, 1983
C	CBA	CHROM ABERR, ANIMAL BONE MARROW IN VIVO	+	0	2.7000	MOHARTY, 1987
C	DLM	DOMINANT LETHAL TEST, MICE	−	0	46.0000	DEKNUDT & LEONARD, 1982

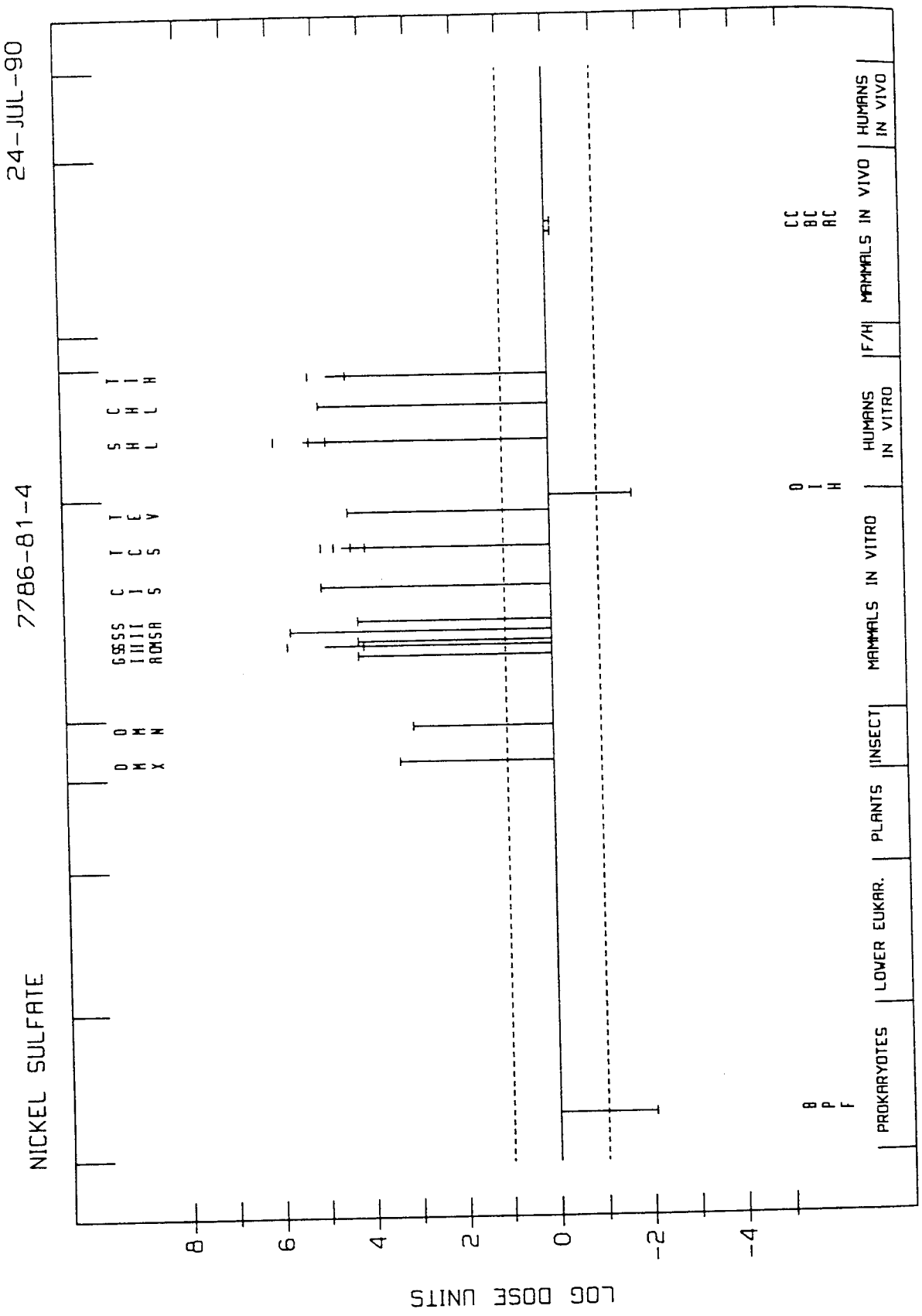
[1]Doses are given as concentrations of the element, not the concentration of the compound.


NICKEL CHLORIDE
7718-54-9
24-JUL-90
LOG DOSE UNITS
8
6
4
2
0
-2
-4
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/HI
MAMMALS IN VIVO
HUMANS IN VIVO

NICKEL SULFATE

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
G	BPF	BACTERIOPHAGE, FORWARD MUTATION	-	0	114.0000	CORBETT ET AL., 1970
G	SA0	S. TYPHIMURIUM TA100, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS ET AL., 1985
G	SA5	S. TYPHIMURIUM TA1535, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS ET AL., 1985
G	SA7	S. TYPHIMURIUM TA1537, REVERSE MUTATION	-	0	0:0000	ARLAUSKAS ET AL., 1985
G	SA8	S. TYPHIMURIUM TA1538, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS ET AL., 1985
G	SA9	S. TYPHIMURIUM TA98, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS ET AL., 1985
G	EC2	E. COLI WP2, REVERSE MUTATION	-	0	0.0000	ARLAUSKAS ET AL., 1985
G	DMX	D. MELANOGASTER, SEX-LINKED RECESSIVES	+	0	45.0000	RODRIGUEZ-ARNAIZ & RAMOS, 1986
A	DMN	D. MELANOGASTER, ANEUPLOIDY	(+)	0	90.0000	RODRIGUEZ-ARNAIZ & RAMOS, 1986
G	GIA	MUTATION, OTHER ANIMAL CELLS IN VITRO	-	0	1.0000	RIVEDAL & SANNER, 1980
G	GIA	MUTATION, OTHER ANIMAL CELLS IN VITRO	(+)	0	6.0000	CHRISTIE ET AL., 1990
S	SIC	SCE, CHINESE HAMSTER CELLS IN VITRO	+	0	0.1700	DENG & QU, 1981
S	SIC	SCE, CHINESE HAMSTER CELLS IN VITRO	+	0	8.0000	OHNO ET AL., 1982
S	SIM	SCE, MOUSE CELLS IN VITRO	+	0	6.0000	ANDERSEN, 1983
S	SIS	SCE, SYRIAN HAMSTER CELLS IN VITRO	+	0	0.2000	LARRAMENDY ET AL., 1981
S	SIA	SCE, OTHER ANIMAL CELLS IN VITRO	(+)	0	6.0000	ANDERSEN, 1983
C	CIS	CHROM ABERR, SYRIAN HAMSTER CELLS IN VITRO	+	0	1.0000	LARRAMENDY ET AL., 1981
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	4.5000	RIVEDAL & SANNER, 1980
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	9.0000	PIENTA ET AL., 1977
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	1.0000	DIPAOLO & CASTO, 1979
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	1.9000	ZHANG & BARRETT, 1988
T	TEV	CELL TRANSFORMATION, OTHER VIRAL SYSTEMS	+	0	4.0000	WILSON & KHOOBYARIAN, 1982
D	DIH	STRAND BREAKS/X-LINKS, HUMAN CELLS IN VITRO	-	0	56.0000	FORNACE, 1982
S	SHL	SCE, HUMAN LYMPHOCYTES IN VITRO	+	0	1.4000	WULF, 1980
S	SHL	SCE, HUMAN LYMPHOCYTES IN VITRO	+	0	0.6000	LARRAMENDY ET AL., 1981
S	SHL	SCE, HUMAN LYMPHOCYTES IN VITRO	+	0	0.1000	DENG & QU, 1981
S	SHL	SCE, HUMAN LYMPHOCYTES IN VITRO	+	0	0.6000	ANDERSEN, 1983
C	CHL	CHROM ABERR, HUMAN LYMPHOCYTES IN VITRO	+	0	1.0000	LARRAMENDY ET AL., 1981
T	TIH	CELL TRANSFORMATION, HUMAN CELLS IN VITRO	+	0	4.0000	LECHNER ET AL., 1984
T	TIH	CELL TRANSFORMATION, HUMAN CELLS IN VITRO	+	0	0.6000	BIEDERMANN & LANDOLPH, 1987
C	CBA	CHROM ABERR, ANIMAL BONE MARROW IN VIVO	-	0	1.3000	MATHUR ET AL., 1978
C	CCC	CHROM ABERR, SPERMATOCYTES	-	0	1.3000	MATHUR ET AL., 1978
I	ICR	INHIBIT CELL COMMUNICATION, ANIMAL CELLS	+	0	60.0000	MIKI ET AL., 1987

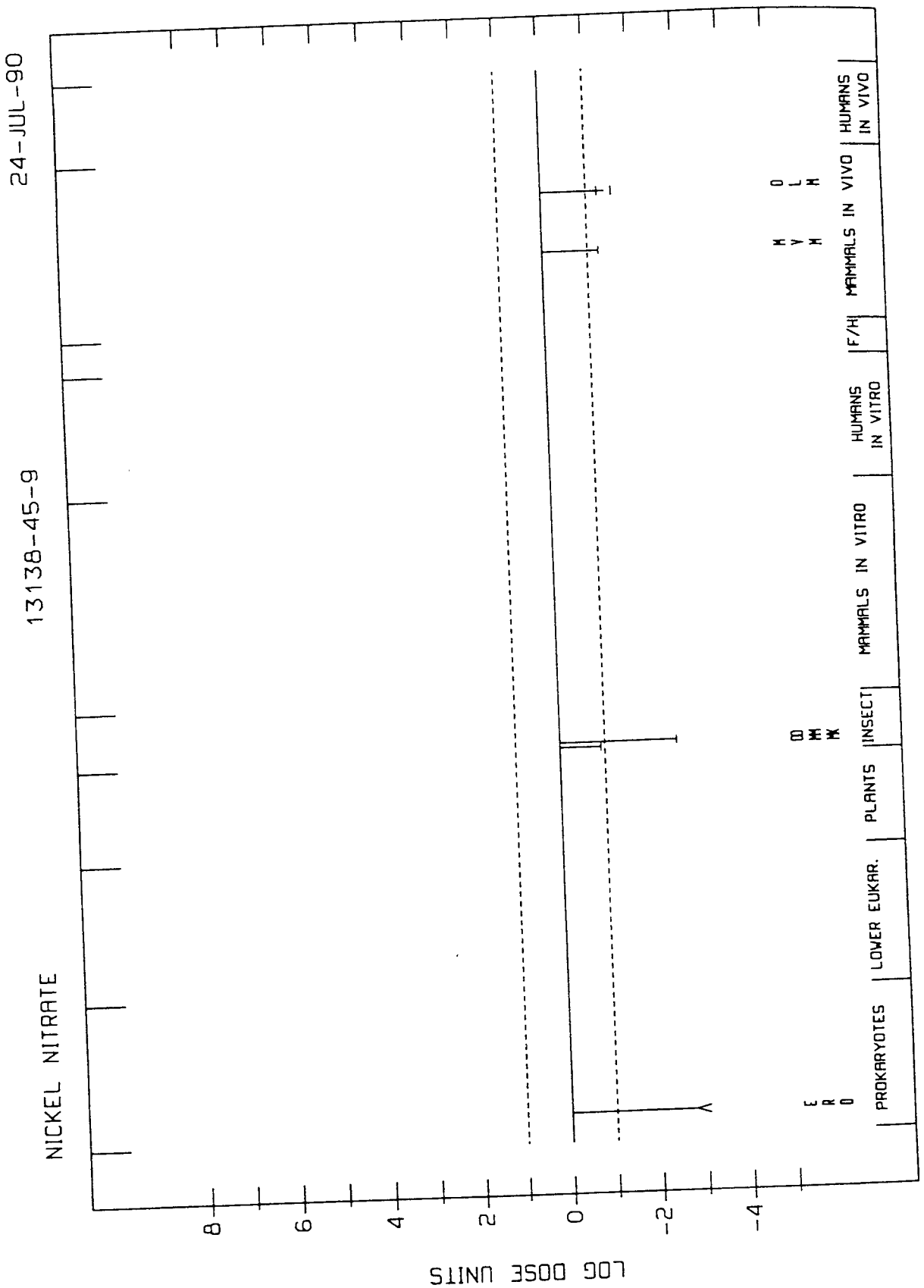
[1]Doses are given as concentrations of the element, not the concentration of the compound.


24-JUL-90
7786-81-4
NICKEL SULFATE
LOG DOSE UNITS
8
6
4
2
0
-2
-4
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/H
MAMMALS IN VIVO
HUMANS IN VIVO
CC
BC
AC
D
I
H
B
P
F

NICKEL NITRATE

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
D	ERD	E. COLI REC, DIFFERENTIAL TOXICITY	-	-	605.0000	DE FLORA ET AL., 1984a
G	SA0	S. TYPHIMURIUM TA100, REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	SA5	S. TYPHIMURIUM TA1535, REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	SA7	S. TYPHIMURIUM TA1537, REVERSE MUTATION	-	-	0:0000	DE FLORA ET AL., 1984a
G	SA8	S. TYPHIMURIUM TA1538, REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	SA9	S. TYPHIMURIUM TA98, REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	SAS	S. TYPHIMURIUM (OTHER), REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	DMM	D. MELANOGASTER, SOMATIC MUTAT/RECOMB	-	0	8.2500	RASMUSON, 1985
G	DMX	D. MELANOGASTER, SEX-LINKED RECESSIVES	-	0	8.2500	RASMUSON, 1985
G	DMX	D. MELANOGASTER, SEX-LINKED RECESSIVES	-	0	407.0000	VOGEL, 1976
M	MVM	MICRONUCLEUS TEST, MICE IN VIVO	-	0	18.0000	DEKNUDT & LEONARD, 1982
C	DLM	DOMINANT LETHAL TEST, MICE	-	0	37.0000	DEKNUDT & LEONARD, 1982
C	DLM	DOMINANT LETHAL TEST, MICE	-	0	18.0000	JAQUET & MAYENCE, 1982

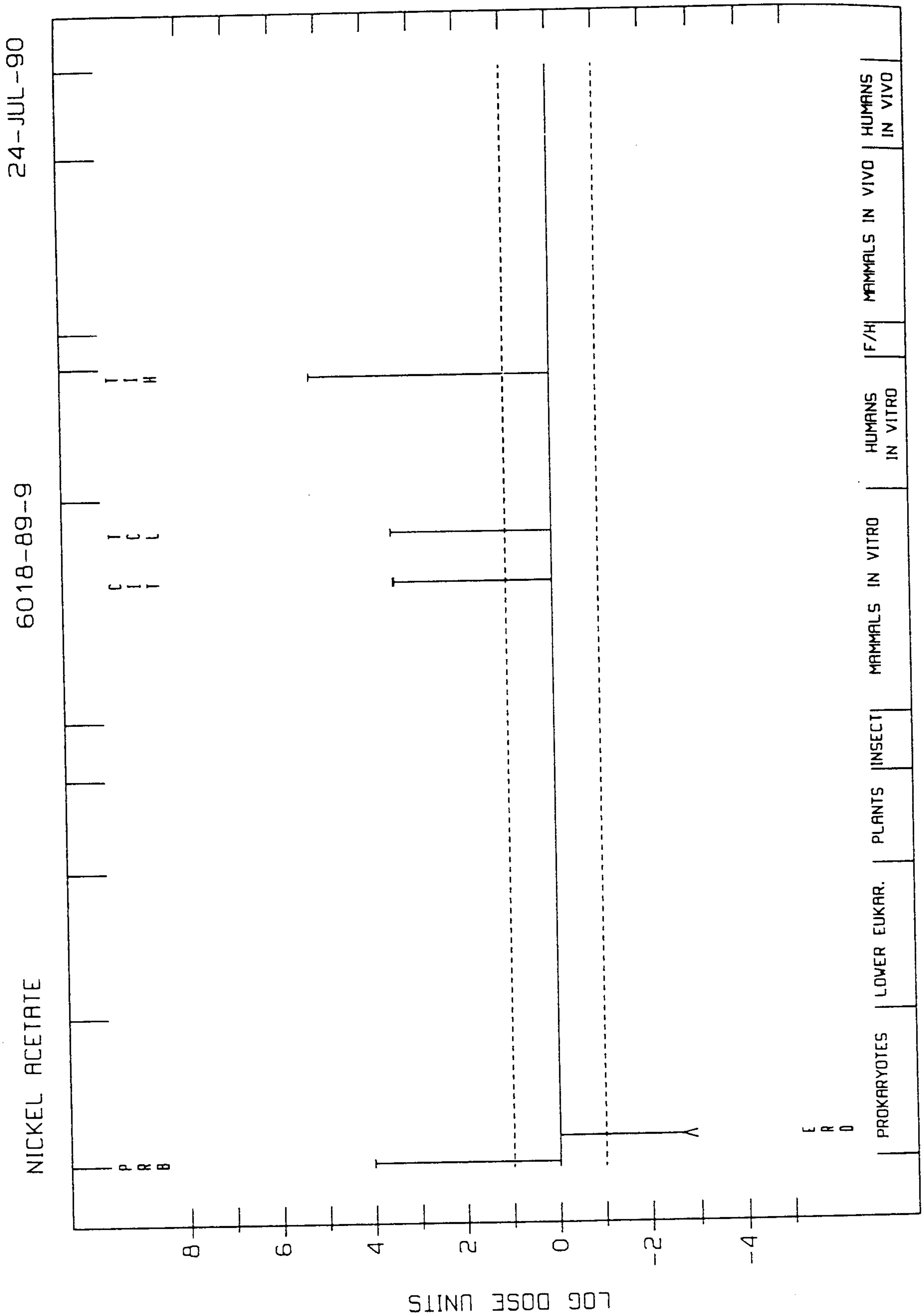
[1]Doses are given as concentrations of the element, not the concentration of the compound.


24-JUL-90
13138-45-9
NICKEL NITRATE
LOG DOSE UNITS
8
6
4
2
0
-2
-4
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/H
MAMMALS IN VIVO
HUMANS IN VIVO
NEGATIVE
EQUIVOCAL
POSITIVE

NICKEL ACETATE

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
D	PRB	PROPHAGE, INDUCT/SOS/STRAND BREAKS/X-LINKS	(+)	0	9.4000	ROSSMAN ET AL., 1984
D	ERD	E. COLI REC, DIFFERENTIAL TOXICITY	-	-	417.0000	DE FLORA ET AL., 1984a
G	SA0	S. TYPHIMURIUM TA100, REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	SA5	S. TYPHIMURIUM TA1535, REVERSE MUTATION	-	-	0:0000	DE FLORA ET AL., 1984a
G	SA7	S. TYPHIMURIUM TA1537, REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	SA8	S. TYPHIMURIUM TA1538, REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	SA9	S. TYPHIMURIUM TA98, REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
G	SAS	S. TYPHIMURIUM (OTHER), REVERSE MUTATION	-	-	0.0000	DE FLORA ET AL., 1984a
C	CIT	CHROM ABERR, TRANSFORMED CELLS IN VITRO	+	0	38.0000	UMEDA & NISHIMURA, 1979
C	CIT	CHROM ABERR, TRANSFORMED CELLS IN VITRO	+	0	35.0000	NISHIMURA & UMEDA, 1979
T	TCL	CELL TRANSFORMATION, OTHER CELL LINES	+	0	33.0000	HANSEN & STERN, 1983
T	TIH	CELL TRANSFORMATION, HUMAN CELLS IN VITRO	+	0	0.6000	BIEDERMANN & LANDOLPH, 1987

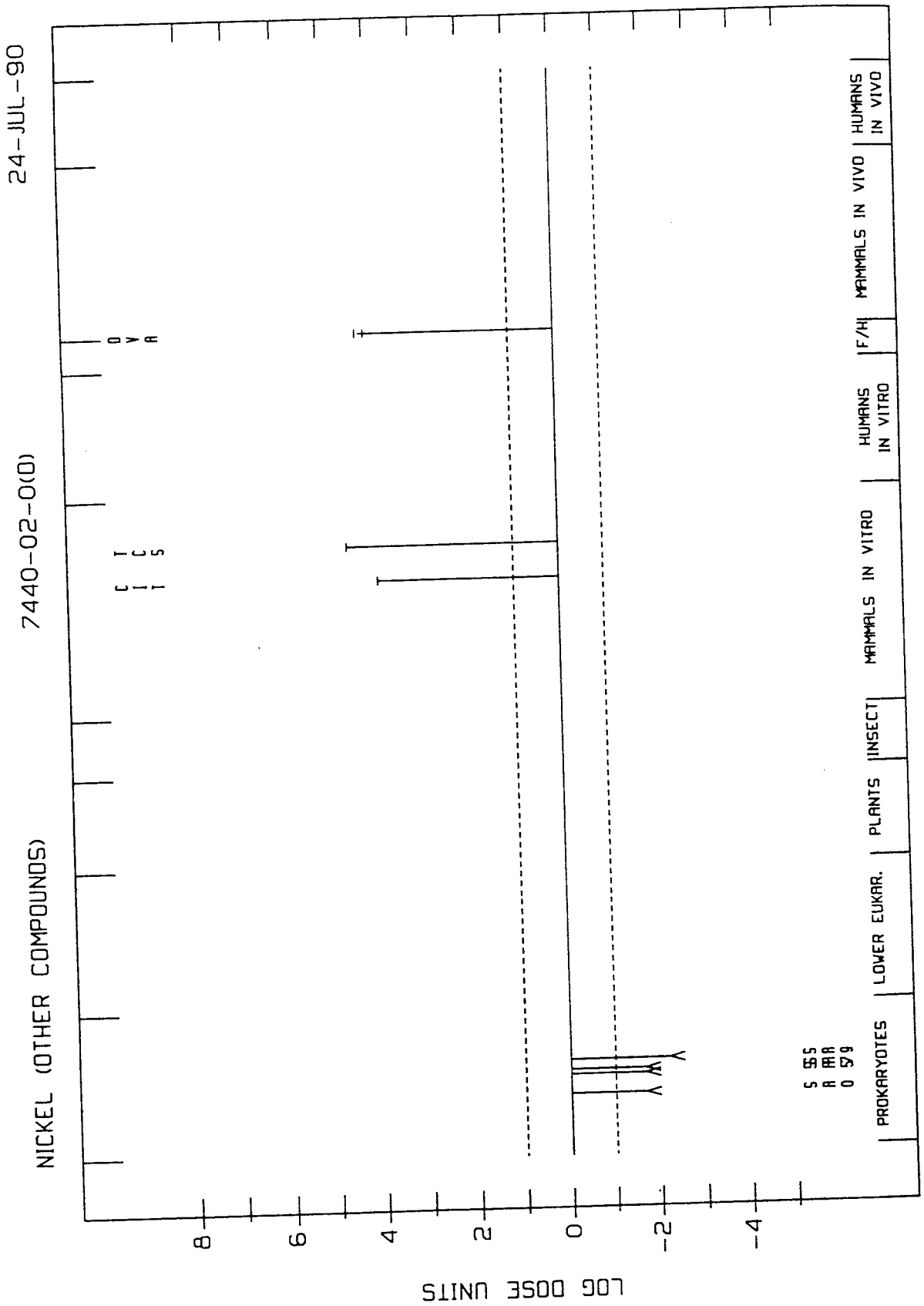
[1]Doses are given as concentrations of the element, not the concentration of the compound.


NICKEL ACETATE
6018-89-9
24-JUL-90
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/H
MAMMALS IN VIVO
HUMANS IN VIVO
LOG DOSE UNITS
8
6
4
2
0
-2
-4
PRB
ERD
CIT
ICL
IIH

NICKEL (OTHER COMPOUNDS)

END POINT	TEST CODE	TEST SYSTEM	RESULTS NM	RESULTS M	DOSE[1] (LED OR HID)	REFERENCE
G	SA0	S. TYPHIMURIUM TA100, REVERSE MUTATION	-	-	50.0000	HAWORTH ET AL., 1983[2]
G	SA5	S. TYPHIMURIUM TA1535, REVERSE MUTATION	-	-	50.0000	HAWORTH ET AL., 1983[2]
G	SA7	S. TYPHIMURIUM TA1537, REVERSE MUTATION	-	-	50.0000	HAWORTH ET AL., 1983[2]
G	SA9	S. TYPHIMURIUM TA98, REVERSE MUTATION	-	-	167:0000	HAWORTH ET AL., 1983[2]
C	CIT	CHROM ABERR, TRANSFORMED CELLS IN VITRO	+	0	12.0000	NISHIMURA & UMEDA, 1979[3]
T	TCS	CELL TRANSFORMATION, SHE, CLONAL ASSAY	+	0	2.6000	COSTA & MOLLENHAUER, 1980c[4]
D	DVA	STRAND BREAKS/X-LINKS, ANIMALS IN VIVO	+	0	5.0000	CICCARELLI & WETTERHAHN, 1982[5]
D	DVA	STRAND BREAKS/X-LINKS, ANIMALS IN VIVO	+	0	7.5000	CICCARELLI ET AL., 1981[5]

[1] Doses are given as concentrations of the element, not the concentration of the compound.
[2] Nickelocene
[3] Nickel potassium cyanide
[4] Nickel subselenide (crystalline)
[5] Nickel carbonate


24-JUL-90
7440-02-0(0)
NICKEL (OTHER COMPOUNDS)
LOG DOSE UNITS
8
6
4
2
0
-2
-4
PROKARYOTES
LOWER EUKAR.
PLANTS
INSECT
MAMMALS IN VITRO
HUMANS IN VITRO
F/H
MAMMALS IN VIVO
HUMANS IN VIVO

APPENDIX B

Report on Carcinogens (RoC), 9th Edition
Review Summary

Report on Carcinogens (RoC), 9th Edition
Review Summary

Nickel Compounds

NOMINATION
Review for possible listing as a *known to be human carcinogen* based on recent IARC reclassification of Nickel and Nickel Compounds as a known human carcinogen (IARC Vol. 49, 1990).

DISCUSSION
Nickel and Certain Nickel Compounds, which have many industrial and commercial applications (including use in stainless steels, nickel alloys, catalysts, batteries, pigments, ceramics, etc.), is currently listed in the RoC as *reasonably anticipated to be a human carcinogen.* Studies of workers exposed to various nickel compounds show the risks for death from lung cancer and nasal cancer are elevated. Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel compounds encountered in the nickel refining industries which included sulfates, which are soluble, and combinations of sulfides and oxides, which are insoluble, are carcinogenic to humans. Both soluble and insoluble nickel compounds are multi-species animal carcinogens by multiple routes of exposure and cause tumors both at the site of application and at distant sites. The combined results of epidemiological studies, carcinogenesis studies in rodents, and mechanistic data support the concept that nickel compounds act by the generation of nickel ions at critical sites in target cells of carcinogenesis and allow consideration and evaluation of these compounds as a single group. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as known to be human carcinogen	7 yes/0 no
NTP EC Working Group (RG2)	list as known to be human carcinogen	4 yes/3 no/1 a*
NTP Board RoC Subcommittee	list as known to be human carcinogen	12 yes/0 no

*a-abstentions

Public Comments Received:
A total of 17 public comments were received:

- 15 against upgrading to a known to be human carcinogen
- 1 recommending listing only insoluble Nickel Compounds as known human carcinogens
- 1 providing comments on the content of the background document prepared for the review of this nomination